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The red skin syndromes: corticosteroid addiction and withdrawal

Marvin J Rapaport[†] and Vicki Rapaport

Chronic, worsening eczematous rash patients are frequently tested and re-evaluated to search for a cause, since they appear to resist treatment with corticosteroids. The patients are usually atopics. Systemic evaluations and various allergy testing coupled with a large variety of topical and systemic medications fail to manage the problem. Typically, the patients initially experience a minimal rash that progresses to a more extensive markedly symptomatic dermatitis despite increasing amounts and strengths of topical and systemic steroids. Various syndromes have been named depending upon the body location involved. In evaluating and treating over 1500 patients it has been ascertained that the worsening problem is due to the therapy, namely corticosteroids, not uncontrollable eczema. Cure occurred in all patients after total cessation of these medications, requiring at times 1–2 years attended by multiple flares of the rash. The mechanism appears to be vascular nitric oxide release. This article delineates in minute detail the typical patterns of addiction, the total evaluation of the patients and the characteristic events of prolonged withdrawal. A study of serum nitric oxide values is included to help in understanding this frequently perplexing disease.

Expert Rev. Dermatol. 1(4), 547–561 (2006)

The intent of this article is to be provocative. Our goal is to help misdiagnosed, mismanaged, mistreated and distraught dermatitis patients. Typically, they have traveled from physician to physician and have suffered for months to years, after beginning with a minor rash that evolved into a severely symptomatic eczematous problem despite multiple evaluations and seemingly appropriate therapy.

Since 1980, when Marvin Rapaport initiated the contact dermatitis and photo dermatitis clinic in the Division of Dermatology at the University of California (LA, USA), referred patients often exhibited peculiar, atypical and bizarre rashes (FIGURE 1). The referring physician asked for the 'hidden allergen' to be found; they believed that a contact chemical was the cause of the worsening rash. Most of the patients were atopics, with very similar histories and clinically demonstrating very distinctive patterns of rash.

These patients had been evaluated and various diagnoses, such as photodermatitis, factitial disorder, allergy to unknown

chemicals, reactions to airborne allergens or an undetected internal problem, were thought to be operative. As the rash progressed with more redness, pruritus and burning, they were treated with increasing amounts and potency of topical corticosteroids and often supplemented with oral and intramuscular corticosteroids. The steroids had offered short-lived relief of symptoms, only to be followed by a more intense flare of the rash as the medication was tapered or stopped. The steroids 'were not working anymore' and this is when they were referred for our evaluation. They were different from other eczema patients.

Material & methods

Since 1980, approximately 1500 eczematous, erythematous patients with distinct characteristics of history and clinical patterns were evaluated, closely observed, treated and followed for many months to years until cure, and then for many years thereafter. They were distinct. They did not have mild eczema, periorbital or

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[†] Author for correspondence
UCLA, 436 No. Bedford Drive
Suite 306, Beverly Hills,
CA 90210, USA
Tel.: +1 310 274 4401
Fax: +1 310 274 5194
rapndad@aol.com

KEYWORDS:
corticosteroids, eczema, nitric
oxide, pruritus, vasoconstriction,
vasodilatation

perioral dermatitis or contact dermatitis. After appropriate dermatological and medical evaluations, only one parameter of treatment was used in all patients – total and absolute cessation of topical and systemic corticosteroids. Only ‘supportive’ care was given for pruritus, pain, erythema, infection and other associated problems. No ‘active’ ‘antieczema’ therapy was given. The patients acted as their own controls, having undergone numerous and diverse therapies for eczema before we began treating them.

Results

Multiple flares of erythema occurred after beginning the total steroid withdrawal. Cure occurred anytime from 4 months to 2 years, depending on how long they had used steroids in the past. Continual follow-up for most patients was from 1 to 20 years after cure. No relapses occurred. Reports of these types of patients appear in the literature with the diagnosis of various named syndromes of unknown etiologies. Our results suggest that none of these ‘syndromes’ are not novel at all but represent only corticosteroid addiction. Our observations of patients who fit into the ‘syndrome’ categories follows. An in-depth description of both the addictive and withdrawal phase is provided. BOX 1 summarizes the major points of the addictive and withdrawal phases.

Syndromes

Various syndromes have been named in the literature for what is purported to be distinct clinical problems. We believe they are all corticosteroid addicted (BOX 2).

Red face syndrome

Red face syndrome was the most common presentation and was seen in over 800 patients. The underlying disease was atopic dermatitis in approximately 95% of the patients and seborrheic dermatitis in the remaining 5%. Frequently, an eyelid dermatitis was the initial complaint. The initiating factors could have been drying and irritation from windy conditions, irritation from eye make-ups or nonspecific pruritis. The rash progressed and worsened as more steroids were used, with larger areas of the face erupting but often sparing the nose and the upper lip (‘the headlight sign’). As the problem worsened, edema of the eyelids and vesiculation of the cheeks occurred, associated with a more severe erythema. The seborrheic patients typically began with blepharitis or typical rash on the cheeks. Their addictive and withdrawal phases were the same as the atopics but withdrawal took less time. This is owing to the peculiar inherited vasoactive features of the atopic. BOX 3 lists instructions in the literature that are offered to patients [1–7].

Post-peel/laser erythema syndrome

A total of 20 patients with post-peel/laser erythema syndrome have been treated. The patients had been given corticosteroids of medium-to-potent strength for routine facial applications immediately after either procedure in an attempt to forestall any keloids or hypertrophic scars. Many months of usage was typical and a few patients were atopics and had used steroids periodically in other body sites before this chronic facial application. Three patients had used steroids for perianal pruritis and nonspecific vulvitis – these areas flared and rebounded with erythema when the face became continually red. Because the patient experienced a burning sensation on the face, the symptom was blamed on the ‘burn’ of the laser or peel. Three patients sought legal redress. BOX 4 lists suggested causes cited in the literature of the erythema and burning [8–13].

Status cosmeticus

Fisher described a group of female patients who were unable to tolerate any cosmetic usage on any part of their face because they experienced a ‘disagreeable’ sensation. A mild erythema of the ‘butterfly area’, in addition to a slight edema of the eyelids, was described. A minor follicular eruption was seen occasionally on the cheeks. All patients had bitter subjective complaints of burning and stinging sensations on a continual 24-h basis and all cosmetics ‘disagreed with them’. Fisher suggested that this was due to an ‘occult’ allergic contact, photo contact or urticarial contact dermatitis. It was suggested that there was a ‘diathesis’ to seborrhea or rosacea because the patients used too many creams. He also believed they were dysmorphic and were experiencing a dermatological nondisease because they were depressed or even suicidal. All patients had been using weak potency topical corticosteroids for months to years because of initial skin dryness or mild skin irritations.



Figure 1. Severe erythema eyelids and face: steroids applied for 11 years. Note normal skin color in preauricular area.

Box 1. Addiction – withdrawal: major points.

- When the patient demonstrates a long-term worsening eczematous rash, despite appropriate therapy, consider corticosteroid addiction as the cause of expanding rash
- All patients have similar histories and show the same clinical picture no matter which body area is involved
- Almost all patients are atopics and the problem usually begins as a small minor patch of eczema
- Severe burning and pain frequently accompany little, if any, pruritis
- The rash does not worsen with soap usage, dry, cold winter weather or exposure to winds, as is typical for atopic dermatitis
- Dust mites, hidden allergens, emotions and sunlight are not etiological factors
- Examine the affected skin for pre-atrophy and atrophy
- Spongiotic dermatitis is often seen on biopsy of the affected skin
- Patch tests are invariably negative or show a few nonspecific irritant false positives (the 'angry back syndrome')
- Patients are not 'allergic' to one steroid preparation, but can use others – false positive patches to corticosteroids occur
- When patients cease using corticosteroids, unique withdrawal patterns are seen – distant rash, edema, vesicles and severe erythema
- Treatment with almost all topicals, including Vaseline, 'burns' when applied to the skin during the early withdrawal phase
- Tacrolimus and pimecrolimus are of little benefit. Burning sensations worsen with their usage
- Seborrheic dermatitis patients with chronic steroid usage on the face demonstrate the same withdrawal symptoms and signs as the atopic
- Physicians administer corticosteroids in ingenious combinations, by various routes, and frequently for the diagnosis of 'eczema'
- Superpotent corticosteroids are sampled widely and often used as initial therapy. They are often used on an ongoing basis despite admonitions to 'stop at 2 weeks'
- Intramuscular and oral corticosteroids are frequently administered when the problem 'rash' worsens or flares
- A lawyer-controlled Steroid Litigation Group exists nationally in the USA
- Consider physiology of atopic skin – vasoconstriction/vasodilatation; dermographism/irritability
- The basis for skin redness in these patients is serum nitric oxide elevations, not atopic dermatitis flares
- Every physician knows about corticosteroid over-usage and side effects, but two to four new patients a month are seen in our office with these addiction problems

We have cared for eight patients with this condition, all of whom were atopics and who presented with a very mild facial erythema but a burning sensation that was disproportional to the degree of redness. Years before being seen, they had all began applying weak strength corticosteroid preparations because of nonspecific itching or dryness, a common complaint of atopics. They never increased the potency of the corticosteroid preparations since some relief was usually obtained. They never evolved into a full red face syndrome since the steroid potency was low.

Physical examination revealed small telangiectasias with a very slight skin atrophy. In addition, rare acneiform papules were seen on the cheeks. One patient had been advised to avoid using her computer since it was believed that the light from the screen was causing this 'photo' eruption. She was referred for photopatch testing. With complete corticosteroid withdrawal the rashes eventually cleared and the stinging and burning vanished in all of our patients. The use of oral tetracycline did not help even though there were

follicular papules. Clearing and cure usually took 6–12 months. BOX 5 lists purported etiologies suggested in the literature [14–16].

Red scrotum syndrome

Approximately 30 patients with a chronic burning erythema in the scrotal, inguinal and penile areas have been treated. They had used corticosteroids in the groin area for 5–15 years, with the initial diagnosis being pruritus or mild erythema due to atopic dermatitis or a nonspecific irritant contact dermatitis. One patient had used corticosteroids in the anal area for 10 years, in the scrotal area for 15 years (both areas had been pruritic) and on the face for 3 years to treat seborrheic dermatitis. He had flared into a full-blown red face syndrome and the groin and anal areas flared with significant erythema. When the corticosteroids were stopped, the face cleared first followed by the anal area 6 months later. There was a persistent erythema in the scrotum and penis for an additional year. This suggests that the

Box 2. Erythema syndromes in literature.

- Red face syndrome
- Prolonged post-peel/laser erythema
- Status cosmeticus
- Red scrotum syndrome
- Vulvodynia
- Perianal atrophoderma
- Chronic actinic dermatitis
- Chronic recalcitrant eczema

All patients should be considered corticosteroid addicted, not part of these unusual syndromes with cause unknown.

area treated longest with corticosteroids takes the longest time to clear when multiple sites have been exposed to steroid applications.

Fisher coined the term ‘red scrotum syndrome’ to describe a group of elderly men who presented with an annoying burning scrotal rash. He noted erythema and telangiectasia prominently on the anterior half of the scrotum, and despite a limited area of skin involvement, the patients complained of severe constant itching or burning and they had to avoid sitting since the pressure resulted in more pain. Because of the normal thin skin in this area, atrophy ensues quickly with steroid usage. Symptoms can persist for a very long period of time, at times not fully clearing. Patients can endure severe psychological depression [17–21].

Vulvodynia

A total of 12 patients with vulvodynia have been seen. All women had been using superpotent topical corticosteroids for 3–18 years. Initially the patients presented to the gynecologist with a nonspecific vulvar irritation (they were all atopics) and were treated with a triamcinolone/nystatin combination cream. Our examination revealed only a mild erythema in the vestibule of the labia majora. Complaints of severe burning are invariably out of proportion to the physical findings. Vulvodynia has been classified into three subsets: vulvovestibulitis (burning, irritation or rawness), essential vulvodynia (burning and rawness spreading from the vulvar vestibule to include the labia majora) and cyclic vulvodynia. At times, subtle erythema and scaling are present. Suggested therapy as noted by a national vulvodynia association includes intralesional corticosteroids with lidocaine, estradiol cream, triamcinolone cream and oral anticandidal therapy. Patients had been placed on elimination diets since yeast infections were suspected. A psychological hysterical component was always suspected. None of these patients had lichen sclerosis et atrophicus or any other distinct diagnosis.

When the patients had been using the corticosteroids for many years it was very difficult to wean them off. Their burning was very severe and relief was only obtained by using more corticosteroids. Routine daily activities could not be readily accomplished.

A similar mucous membrane steroid addiction can occur in corticosteroid-treated cheilitis patients. Mouth breathing dries the lower lip and then steroids had been prescribed for relief. We have seen seven patients with this problem who had sought care from dentists, oral pathologists, dermatologists and allergists. Three of them had been treated for chronic sunlight damage only for the problem to worsen after using topical 5-fluorouracil. The patients cleared and remained asymptomatic in 8–12 months after stopping the corticosteroids. No atrophy was noted [22–27].

Perianal atrophoderma

We have treated ten patients with persistent anal erythema and burning. They had all used topical corticosteroids for 1–12 years and four had been given systemic corticosteroids, when the itch and burn worsened. Goldman and Kitzmiller noted persistent usage of fluorinated corticosteroids for up to 11 years in their eight patients. All of their patients exhibited pruritis and atrophy and six out of the eight demonstrated telangiectasias. They could not be weaned off the corticosteroids. All of our patients were atopics. Six patients were cured after 6–10 months. The other four could not stop using the steroids, as the flares were so severe. BOX 6 summarizes proposed etiologies for groin and anal problems as cited in the literature [28].

Chronic actinic dermatitis

We have seen 12 patients who exhibited this erythematous, eczematous rash in a photo distribution – the face, frontal neck and extensor surfaces of the arms and hands. They had all been diagnosed as photosensitive and had been treated with cessation of sun exposure, continual indoor and outdoor sunscreen usage and on two occasions with systemic immunosuppressive agents. All were chronic corticosteroid users both topically and systemically. Our patients experienced burning and itching

Box 3. Facial erythema patient instructions from literature.

- Avoid make-up
- Avoid airborne chemicals
- No perfume usage
- Change eye glasses
- Don't handle chemicals and foods
- Change all hair preparations
- No hair-dye usage
- No food with preservatives to be ingested
- Change pillows
- No sun exposure
- Avoid long exposures to computer screen
- Avoid intense lighting in house

Box 4. Laser/peel erythema causes suggested in literature.

- Untrained MD
- Wrong laser
- Wrong dressing
- Too many passes with laser
- Sun exposure
- Prior Retin-A usage
- Hidden infections
- Allergy to sunscreens

throughout the year but symptoms often increased during warm weather (when UV was stronger), with exercise or when exposed to high indoor temperatures (kitchen cooking). Several patients' rashes worsened during the winter months. Patch testing gave inconsistent and irrelevant results and photo-patch testing was not performed because of the extreme skin irritability during the patch-test procedure. Six of our patients cleared after periods of 9–16 months and remained clear for 1–6 years in follow-up. Three patients resumed steroid usage and the other three were not followed. Combination UVA/UVB therapy was given to all patients and benefit was often noted. This syndrome has been described as an immunological problem being similar to actinic reticuloid. We have not seen any patients who were truly sensitive to the sunlight. Most of our patients exhibited the headlight sign – clinically not consistent with photosensitivity. We believe that corticosteroid addiction is the sole diagnosis of all patients in the literature [29–37].

Chronic severe eczema

Approximately 300 additional patients were seen who had used corticosteroids chronically on various other body sites and experienced unusual patterns of rash during their withdrawal phases. When rash occurred on legs, severe edema sometimes occurred.

No cardiac or renal disease was uncovered and as the rash cleared, the edema subsided. Diuretics were not totally curative. These patients are referred to as 'awful atopics'.

The withdrawal patterns for all of the syndromes are listed in BOX 7. Various patients' unusual rashes are seen in FIGURES 2 TO 10.

Addiction phase histories

*"Listen to the patient – they will give you the diagnosis",
Sir William Osler*

Other than the few facial seborrheic dermatitis patients, all of those included are atopic individuals who have manifested symptoms of asthma, hay fever or eczema in youth. In addition they can exhibit nonspecific pruritus, urticaria, 'summer allergies', exercise asthma, soap intolerance, itch when wearing wool clothing or a family history of atopy.

The histories are very similar regardless of whether the initial problem is eyelid dermatitis, pruritic groin rash, mild dry eczema on the legs or a slight flare of numular eczema on the body. Initial treatment is often the use of nonprescription weak-strength hydrocortisone creams. With continuing or worsening symptoms, consultation with an MD results in a prescription for a mid-strength topical corticosteroid cream or ointment being given. Rash clears but a recurring and worsening itch or rash is experienced and more frequent cream usage occurs. The addiction sets in after 4–6 weeks of frequent usage. Further medical care is sought because the creams are unsuccessful and the rash is spreading. A superpotent topical corticosteroid is then prescribed and rebound erythema occurs more quickly. Oral prednisone and IM triamcinolone is then used. The episodes of pruritic redness are now accompanied by a burning sensation, which becomes continual. Distant sites erupt with 'eczematous' patches. Being frustrated by the worsening problem, the physicians undertake evaluations with patch and other allergy testing. If a minor reaction patch-test reaction of one or two plus intensity occurs, then that allergen is assumed to be the culprit chemical causing the rash. Allergens, such as captan, fragrances, potassium dichromate or nickel, were at times found to be positive and the patients were sent on a search to avoid any and all contact with these substances. If the rash persisted or worsened despite appropriate medications then it was assumed that the patient had inadvertently exposed themselves to these allergens.

This confusing clinical picture prompted more consultations and tests. Systemic evaluations for underlying collagen vascular disease, flushing syndromes, tumors and metabolic problems were undertaken. Multiple skin biopsies were performed, yielding only nonspecific results. A 'spongiotic dermatitis' was seen and differential diagnosis included contact dermatitis, fungal infection, Grover's disease and an array of nonspecific dermatoses. On occasion, a minimal elevation of the very sensitive antinuclear antibody (ANA) test led the physician to consider a collagen vascular disease (I have treated three patients who carried the false diagnosis of lupus erythematosus or dermatomyositis for 3–7 years. They had been prescribed plaquenil, methotrexate, cyclosporine, azathioprine, IV immunoglobulin, Cellcept® and methotrexate in addition to topical and systemic corticosteroids when the rashes became widespread). With the introduction 5 years ago of the topical immunomodulators,

Box 5. Status cosmeticus causes cited in literature.

- Emotional
- Hidden allergen
- Spouse's aftershave
- Perfume
- Airborne allergens
- Inherited tendency

Box 6. Scrotum–anal–vulva causes cited and remedies from literature.

- Avoid perfumed toilet paper
- Nickel ingestion is the cause
- Clothing is the allergen
- Spouse's candidiasis is transferred and problematic
- Spicy foods are the cause
- Change diet completely
- Emotional factors are operative
- Avoid sweating

tacrolimus and pimecrolimus, widespread usage occurred but with little benefit reported. Off-label usage of some of the new biologicals has also occurred recently.

Since many patients were taking multiple drugs for other problems, such as hypertension, cardiac problems, renal disorders or chronic gastrointestinal upsets, the treating physicians often deleted and substituted many of these drugs, feeling that the rash could be a dermatitis medicamentosa. This strategy also did not work. In addition, these patients visited multiple therapists, such as acupuncturists, holistic physicians and alternative medicine physicians, in addition to searching the internet for new ideas and answers.

There is picture evidence of only one patient evolving during the early addictive phase. She came to the office with severe dermatitis, erythema and burning of the face (FIGURE 2A). She had been seen 8 years prior at the Contact Dermatitis Clinic at UCLA, at that time with a 3-year history of eyelid dermatitis that had been continually treated with topical corticosteroids (FIGURE 2B); she did not follow advice to stop steroid usage. Her work took her to many cities over the next 8 years and she consulted several physicians, always receiving more and more corticosteroids topically and systemically. It took 2 years of steroid withdrawal before she was cured and she has remained clear for the past 9 years (FIGURE 2C).

Initial evaluation of the addicted patient

“Fashion in therapy can have some justification, fashion in diagnosis have none”, Herrick/Tyson

On the first visit, the patient is asked the exact history of the problem and prior management. When did it start? Where did it start? What did it look like? Were there any associated symptoms? What medical treatment have they received? The amount of corticosteroids used. History of flares. General medical problems. What did the patient think was the cause of the problem?

The total body is examined to gauge the extent and morphology of the rash. Some patients exhibited no rash on the first visit since they had just been treated in the prior 2–3 days with intramuscular or oral corticosteroids.

A patch test with 40 of the most common allergens is applied to the back. These allergens include corticosteroids, preservatives, metals, fragrances, rubber preparations, sunscreen agents, adhesives and medicaments (BOX 8). The tests are read at 2 days with a delayed reading 1 day later. Other reports discuss the merits of patch testing in similar patients [38–40].

If indicated, other tests might be performed, such as fungal cultures, skin biopsies and blood studies for collagen vascular diseases or underlying systemic metabolic problems. Endocrine studies have been ordered rarely. Two patients out of over 1500 exhibited extreme tiredness as the withdrawal phase entered the second month and urine and blood endocrine studies were obtained. The studies were normal in both patients and the tiredness cleared in a few weeks with a specific therapy. Addison's disease, glaucoma, osteonecrosis of the hip and diabetes mellitus has not been seen in any of our patients, although these eventualities have been cited in the literature [41–43]. On this first visit, after an in-depth explanation, all corticosteroid usage stops, both topically and systemically. There is no 'step-down' phase, since the vasoconstriction and vasodilatation would continue no matter how low the potency of the corticosteroids used, so the overall problem would not be helped [44–46].

No therapy other than ice compresses are given until the patch tests are read. Our patients have failed to exhibit a true positive that was indicative of allergic contact dermatitis. Nonspecific 'positives' to nickel, cobalt, fragrance mixture, potassium dichromate or merthiolate have been frequently seen. In addition, an 'angry back' can occur due to nonspecific irritation from tape and the allergens in a very irritable skin. On a rare occasion, a 'positive' to a corticosteroid has been seen, but in follow-up weeks later repeat patches were negative. We believe this is a red vasodilatation, not allergy to the steroid. Almost 90% of the patients show a positivity to nickel sulfate, which is typical of atopics. Only some show clinical manifestations of nickel allergy.

Patch testing is performed to search for the 'hidden allergen' but also for future guidance. The patients will use lubricants, moisturizers, make-ups, etc., in the future and they will always wonder if they are 'allergic' to the new cosmetic. With negative

Box 7. Chronic severe eczema patterns of rash seen during withdrawal.

- Erythema
- Atrophy
- Local spread
- Distant spread
- Edema
- Nummular patches
- Burning – eyelids, vulva, lips
- Vesiculation

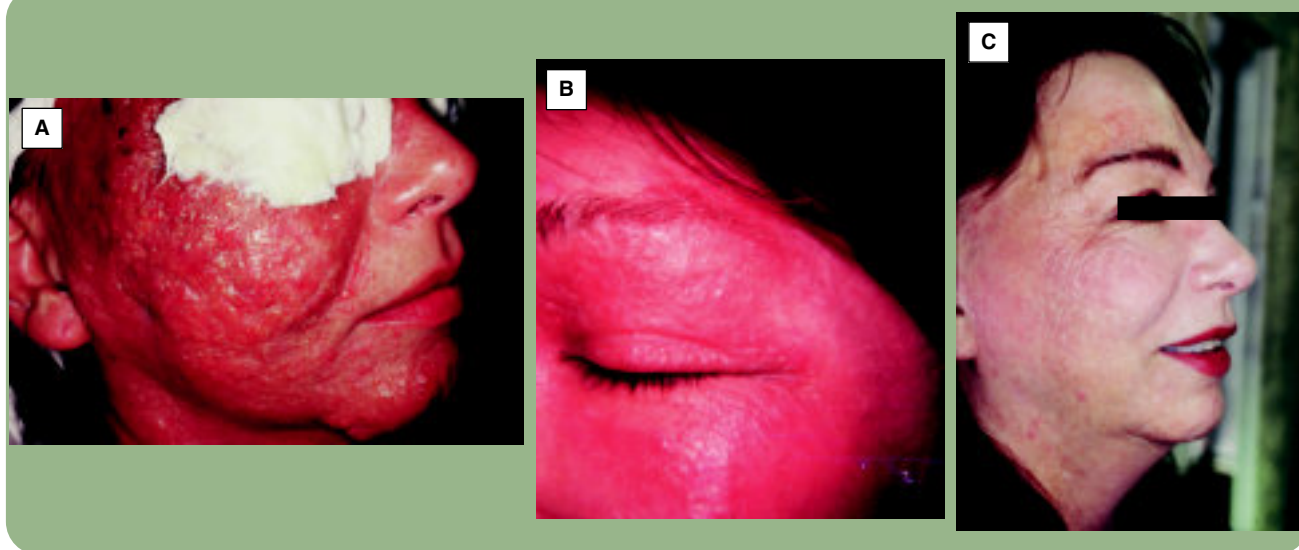


Figure 2. (A) Erythema eyelids and cheeks, normal skin preauricular area, erythema neck and chest, steroids applied for 4 years. (B) Eyelid dermatitis 8 years prior – steroids applied for 3 years. (C) Normal skin 8 years later.

patch tests, which include preservatives, fragrances and other chemicals used in lubricants, we can reassure them that there will be no allergy to any future preparation.

Several papers have suggested the possibility that these ‘red people’ have latex allergies, allergies to dust mites, allergies to dental metals in the mouth or possibly to a specific corticosteroid. However, we believe that this is not supported scientifically and it will be discussed later in this article.

Withdrawal phase management

“Habit is not to be flung out the window by any man, but coaxed downstairs a step at a time”, Mark Twain

It should be noted that during the addictive phase many patients experience mini-withdrawals. When they had visited their physician, especially when beginning a flare, immediate therapy in the form of strong and or topical systemic corticosteroids had been given and the withdrawal phase was never fully manifested. During these mini-withdrawals, erythema and burning occurred – a harbinger of what would happen during total withdrawal.

It is strongly emphasized to the patient that, from day 1, no corticosteroid usage of any kind is tolerated. Cure with total cessation of rashes, total cessation of flares and total cessation of any and all therapy will occur in 6–24 months. All of the patients who stay with this program of total cessation of corticosteroids have been cured. When there has been no flare for 4–6 weeks, the process is usually complete. Approximately 5% of the patients have been unwilling to tolerate the flares or have been unconvinced that this is the proper approach to the problem and they have been lost to follow-up. Enduring the flares can be exceptionally difficult for some patients.

All the patients report similar rash patterns no matter which body area is involved. The initial erythema subsides but within 7–14 days another flare of redness occurs in the same location, at times accompanied by edema (worse in dependent areas, such as legs and eyelids).

The best and most reliable therapy at this point is ice and cool water compresses applied to the affected area, since patients experience a severe burning sensation due to the



Figure 3. (A) Eyelid dermatitis with blepharitis: steroids topically and conjunctivally for 5 years. (B) Distant nummular patch seen on first visit. (C) Spread of rash on cheeks 6 months later.

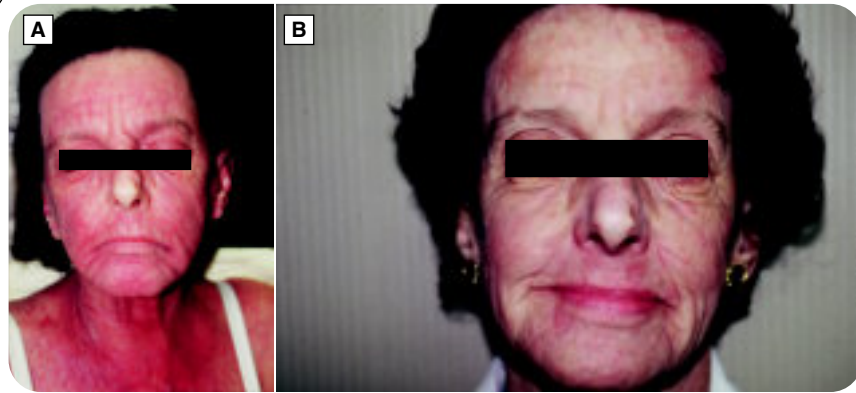


Figure 4. (A) Eczema beginning on legs 25 years prior: steroids and body suit used for 20 years. (B) Clearing 3 years later.

rebound vasodilatation. In the early weeks the patient's skin does not tolerate any creams, lubricants or lotions – even Vaseline causes burns on application. The new immunomodulating topical agents are of no value.

If pain, anxiety or insomnia occurs, analgesics, sleeping pills and anti-anxiety medications are prescribed. At this early phase of the withdrawal there are many phone contacts by staff to monitor and reassure the patient. This psychological support is essential, especially when the burning is severe and if the skin is very red. At the end of this episode of flare (5–10 days), peeling and exfoliation occur. Clear skin can be seen for 1–2 weeks only to be followed by a more severe flare at the same site. Rash usually spreads locally, especially when patients have used steroids for long periods of time (eyelid rash progresses to involve the whole face). Distant sites, such as arms, trunk and legs (where no steroids had ever been applied), can also erupt with erythema and 'eczematous' patches. Bathing with oatmeal oilated bath powder soothes the itching and burning skin. Another one or two severe episodes can occur in the next 4–8 weeks. Sometimes there are no episodes, but continual redness, edema and scaliness for many weeks. If the burning is severe, gabapentin is prescribed. Usually the erythema severity is concomitant with the severity of the burning but at times it can be discordant (mild redness to severe burning; severe redness – mild burning).

In those patients with prolonged prior steroid usage, marked edema and vesiculation can occur in 2–4 months. This is a manifestation of the continual dilatation of the vasculature. Skin biopsies usually show a spongiotic dermatitis pattern with increased vessel formation. If the edema is severe, furosemide is prescribed but only limited benefits occur. Concern about secondary infection can be corroborated

by cultures but empiric usage of antibiotics, such as cephalexin, is used. Burow's solution compresses can quickly dry up the extensive vesiculation.

A peak in severity occurs by 4–6 months. The flares now begin to lessen in severity and duration. The 'good times' (interflare phases) become longer. If the addiction occurred over many years, then the withdrawal phase can go on for 12–24 months. The distant areas do not manifest rash anymore, only the original long-term, steroid-treated sites recur but with milder eruptions.

If there is prolonged severe unrelenting redness and rash, oral cyclosporin has been used at a dosage of 200–500 mg/day for up to 2–3 months. Even though the pathology is vasodilatation, there is an eczematous component and benefit has occurred, in a moderate fashion.

BOX 9 lists the various therapies used through phases of the withdrawal. We believe that the prolonged nature of the vasodilatation is driven by continual or intermittent nitric oxide (NO) release in the vasculature.

NO study during withdrawal

Prolonged topical corticosteroid usage initiates vasoconstriction in the skin followed by a rebound and fixed vasodilatation. NO is the suggested mediator [47,48].

NO or endothelium-derived relaxing factor (EDRF) is an important mediator of immunity and inflammation, in addition to its vasodilatory effects. Three different NO synthase isoforms have been isolated. NO measurement is difficult owing to its brief half life, therefore nitrates and nitrites, stable end products of NO metabolism, are used as markers.

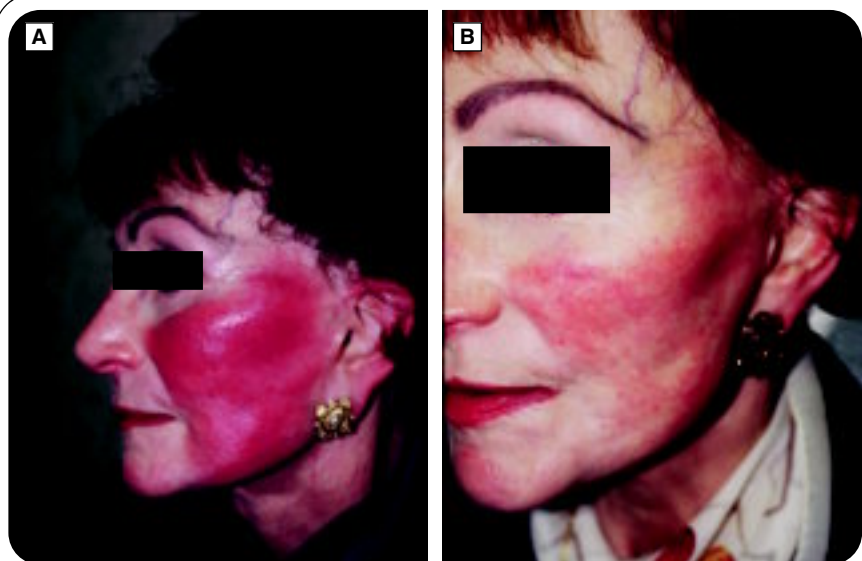


Figure 5. (A) Laser resurfacing of nasolabial folds only: superpotent steroids used for 3 years – severe burning, suicidal. (B) 4 months later – significant clearing; burning sensation persisted.



Figure 6. Pruritic skin: superpotent steroids. 18 60-g tubes applied for 1 year – edema and vesiculation.

Materials & methods

A total of 38 consecutive patients with corticosteroid addiction were entered into the study in 2002. They were designated the addicted group. These patients had been using increasing amounts and strengths of both topical and systemic corticosteroids anywhere for 1–10 years for an original diagnosis of eczema. Control groups consisted of: a group of 26 previously addicted, but now cured patients, designated the cured group – this group exhibited the same histories and course, observed by us, of the addicted patients but had experienced no flares of erythema or eczema for the prior 1–7 years (all of the first 26 patients called agreed to participate with no hesitation); a group of 20 patients with untreated mild eczema of less than 2 weeks duration, called the eczema group. Typical rash consisted of mild eyelid dermatitis, nummular patches on the legs or small eczematous patches on the trunk, present for only 1–2 weeks. No previous eczema had occurred in the prior year and no steroids were used for any reason. It was determined by the statistician that the number of patients in each group was sufficient for the analysis.

The addicted group ceased corticosteroid usage on day 1 of the study. Peripheral bloods were drawn on that day and thereafter at random times until cure occurred. The cured group had bloods drawn upon entry into the study and then again randomly over 2–6 months. Blood samples from the eczema group were taken on day 1 visit and then also randomly as they were followed and treated. All patients were entered into the study within 4 months.

After informed consent was obtained, whole blood samples were drawn from a peripheral vein after an overnight fast. The serum was centrifuged and kept at 20°C. It was transported in cold packs by a local laboratory to the General Medical Services Laboratory in Willow Grove (PA, USA) for analysis.

A quantitative method for the simultaneous measuring of nitrite and nitrate in biological specimens was used. Serum samples were put through a centrifuge ultrafiltration filter after dilution of deionized water. The filtrate was then injected into a Dionex DX-500 ion chromatograph instrument with an ION-PAC AS-14, an analytic and guard column. The detection and quantitation of the nitrate and nitrite was accomplished by using a UV detector [49–55].

Normal values for serum nitrate are 0.25–2.8 µg/ml and for serum nitrite are 0.06–0.6 µg/ml. From other sources, the reference laboratory performed 248 serum nitrate/nitrite assays in the study year, 2002, for environmental and workplace exposures. Elevations were seen in patients taking cardiac medications, nitroglycerin and isorbate nitrate. The laboratory reported no known false positives or negatives. Under this assay, all nitrite levels were zero and only the nitrate assays showed positivity. TABLE 1 summarizes the highly significant results. The addicted group had 70 elevated nitrate levels in 144 specimens, 20 patients showing elevated values, while 18 patients had results in the normal range. Interestingly, of these 18 patients, 13 showed minimal erythema but did have atrophic skin and only smaller nummular oozing skin patches associated with a burning sensation.

In the cured group, only two patients showed elevated values out of 42 specimens. One patient failed to inform us that he was taking nitroglycerin and isorbate nitrate for cardiac disease, which we believe accounted for the elevations in his assay. He was not included in the statistical analysis. In the eczema group, four patients with five elevated values were noted in 29 specimens. Statistical analysis was undertaken for the results of the first test upon entry into the study for each person in the three groups. It should also be noted that most specimens in the cured and eczema groups showed zero levels for nitrates, whereas many normal tests in the addicted group did show low but positive amounts of nitrate.

The evidence is strong that the addicted group had a higher mean than the cured and eczema groups ($p = 0.0001$). There is no evidence that there is any difference in the means of the cured and eczema groups. There is evidence that the red addicted patients have a higher mean nitrate level than the non-red addicted patients. Results from the t-test and the Wilcoxon

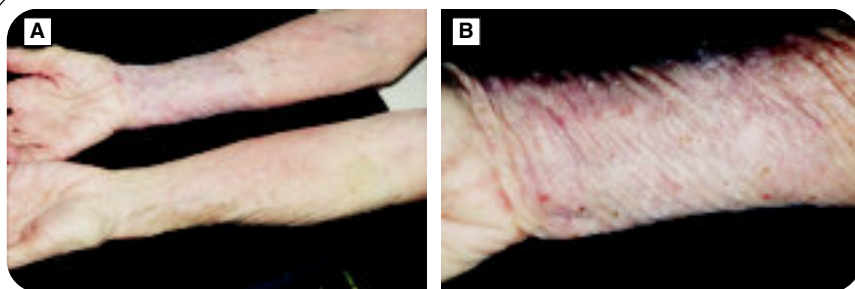


Figure 7. (A) Atrophy right arm after 8 months of topical, oral and intradermal steroids – Colles fracture and cast caused irritant dermatitis initiated therapy in this atopic individual. Atrophy occurred 9 months after steroid cessation. **(B)** Atrophy of skin and fat repairing 3 months later.

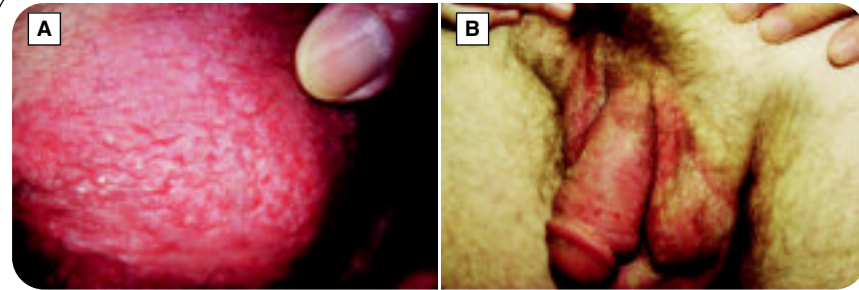


Figure 8. (A) Red scrotum – steroids applied for 3 years for pruritis. (B) Clearing of rash and burning 1 year after steroid cessation.

test were very similar across all tests. We can have confidence in our results as the Wilcoxon test is robust against the deviation from normality that occurs in our data due to skewness and a large number of tests results with zero nitrate level.

Nitrate levels were also elevated temporally in the addicted group. The withdrawal time for each patient in the addicted group was partitioned into 25% increments (early, early-mid, late-mid and late phases) and the percent of elevated nitrate levels during each phase was tabulated. As an example, if the patient took 1 year to be cured, then each phase was 3 months. In the early withdrawal phase, 34% of specimens were elevated but 56% of specimens were elevated during the early-mid and late-mid phases. As the patients neared cure, levels began normalizing, decreasing to 33% positivity and then eventually to normal levels.

We were unable to specifically pinpoint a time relationship between an elevated NO level and the presence of a flare or a prediction of a flare. The addicted patients exhibited random flares that lasted anywhere from 3 days to 3 weeks. The NO levels would, at times, be elevated during these flares and sometimes not. Eventually the NO levels normalized as the flares decreased in severity and length of time and finally ended. To date, all patients are clear with normal NO levels, just like the patients in the cured group. The following are histories of two patients from the addicted group with their NO levels tabulated during their course (TABLE 2).

Case 1

A 54-year-old male developed hay fever in youth. He was hospitalized 6 years prior to being seen by us, for a blood clot in his left leg. During the hospitalization, he began experiencing pruritus on his back. No specific diagnosis was made and he was prescribed the superpotent topical corticosteroid, clobetasol. Over the next 6 years he continued the use of clobetasol for not only pruritus but for a generalized spreading dermatitis. When this dermatitis worsened, he received numerous intramuscular injections of triamcinolone 40 mg and several courses of oral prednisone, up to 80 mg/day for 7–10 days each time. When first seen by us, his legs were edematous and he had a generalized body erythema with vesiculation and oozing. There was a marked palmar and plantar keratotic eczematous dermatitis. Total cessation of corticosteroids resulted in several severe flares

of erythema over the next 10 months, but he improved with shorter flares of erythema, followed by longer periods of clear skin. His serum nitrate levels were elevated throughout, but became lower as he improved. He has been clear from all outbreaks and his NO levels have remained normal for the last 2 years (TABLE 2).

Case 2

A 72-year-old female began having an eyelid dermatitis 20 years prior to being seen. Despite applications of medium to superpotent strength topical corticosteroids for years, the rash spread to involve her entire face, upper extremities and chest. Several intramuscular injections of triamcinolone and courses of oral prednisone were also prescribed during the most recent 5 years. After cessation of the corticosteroids, cure occurred in 16 months. She experienced several flares of erythema on her face and body. She demonstrated elevated nitrate levels in the initial specimens but produced normal levels in the third and fourth quarters of her withdrawal phase. She has remained clear of all eczematous rashes with normal nitrate levels for 2 years (TABLE 2).



Figure 9. Edema and vesiculation of face 3 years after steroids – topically and systemically – used for ear and eyelid rash.



Figure 10. Eczematous, weeping dermatitis 10 months after stopping steroids. Problem began with nipple dermatitis in an atopic who had undergone breast augmentation. Implants were removed 6 months later after continual systemic and topical steroids did not help a worsening generalized body eczema.

Discussion

“One of the first duties of the physician is to educate the masses not to take medicine”, Sir William Osler

This article is not to be construed as an admonition against the use of corticosteroids. This is a powerful medication when appropriately utilized in specific time frameworks and for very specific diagnoses.

Practicing physicians should be aware of unusual problems and observations seen with steroid usage; the common side effects are not addressed in this paper. When steroids are chronically applied to young skin – up to teen years – curious and bizarre atrophies can occur. We have seen striae in the groin in a 15-year-old female who had applied corticosteroids for 4 months to her lower back for ‘psoriasis’ (diagnosis proved to be eczema). A 13-year-old male had applied a moderate strength corticosteroid lotion for 1 year to his back for a non-specific dermatitis and he developed disfiguring striae in the axillae and groin [55].

Overusage of steroids locally has caused ‘disappearing’ fingers and limbs [56,57]. We have seen three patients with this phenomenon (two patients with chronic paronychia and one patient with a Colles fracture cast-induced irritant dermatitis). All three had used large amounts of topical and systemic steroids.

Widespread systemic steroid usage goes on for a variety of inflammatory processes. When a small group of dermatologists were telephone surveyed by us as to the usage of intramuscular triamcinolone, there was a range of no usage to 120 injections per month. A total of 80% of the physicians used intramuscular steroids on a frequent basis.

Approximately 300 patients treated with corticosteroids but exhibiting worsening rashes have been reported as being ‘allergic’ to one or more corticosteroid formula. Most of the patients, when described, were atopic individuals and the reports were based solely on patch-test results [58–67]. There was little, if any, follow-up nor repeat patch testing. This

Box 8. Patch test chemicals.

- Balsam of Peru (perfume)
- Benzophenone (sunscreen)
- Budesonide (corticosteroid)
- Cetylstearyl alcohol (vehicle/emulsifier)
- Cinnamic aldehyde (perfumes/flavors)
- Clobetasol-17-propionate (corticosteroid)
- Diazolidinyl urea [Germall ii] (preservative)
- Epoxy resin (adhesive)
- Formaldehyde (preservative)
- Hydrocortisone 17 butyrate (corticosteroid)
- Isopropyl myristate (emollient/solvent)
- Methyl methacrylate (adhesive)
- Neomycin sulfate (OTC medicine)
- 4-aminobenzoic acid (sunscreen)
- Paratertiarybutyl phenol form (BPF resin)
- 4-chloro-3,5-xylene (chloroxylene; preservative)
- PPD mix (rubber)
- Quaternium (preservative)
- Thiomersal [Merthiolate] (preservative)
- Tixocortol (corticosteroid)
- Benzocaine (OTC medicine)
- Bronopol (preservative)
- Carba mix (rubber)
- Chloro-isothiazolin (preservative)
- Cobalt (metal)
- Colophony (adhesive)
- DMDM hydantoin (preservative)
- Escalol 507 (sunscreen)
- Fragrance mix (perfume)
- Imidazolindinyl urea [Germal 115] (preservative)
- Mercapto mix (rubber)
- Naphthyl mix (rubber)
- Nickel sulphate (metal)
- Paraben mix (preservative)
- Parsol MCX [methoxycinnamate] (sunscreen)
- Potassium dichromate (metal)
- Propylene glycol (vehicle/emulsifier)
- Sorbic acid (preservative)
- Thiuram mix (rubber)
- Wool alcohols (vehicle)

Box 9. Therapy.

- Total corticosteroid cessation
- Ice or cold water compresses continually
- Multiple reassuring and supportive phone calls and visits
- Hydroxyzine – when pruritic
- Antibiotics when secondary infected
- Sleeping pills – when restless
- Tranquilizers – when anxious
- Analgesics – when pain or burning are severe
- Aveeno baths
- Burow's compresses
- Mild lubrication when exfoliating
- UVB therapy 1–2 per week when flares subside
- Cyclosporin – if severe and widespread
- Neurontin – if skin has burning sensation
- Nizoral cream – diluted
- Tacrolimus/pimecrolimus – of little help

'allergy' has not been our experience. We believe that the redness seen in the positive patch reaction is vasodilatation not allergic contact dermatitis.

The described patch results are often mild 1+ or 2+ and do not intensify on delayed reading. In one study, 8% of patients were 'allergic' to tixocortol, a 'marker' for steroids. This is an extremely high number not supported by my testing in over 3000 patients. We have seen only one positive and this disappeared on repatching a few weeks later. In the papers, some patients were 'allergic' to one topical steroid preparation but not to others. What are reliable criteria for differentiating irritant from allergic reactions (or is this autoimmunity?) [68] in such patients and how do we separate out steroid erythema? A few of our patients showed a rare positive red patch to corticosteroids during early flared phases of withdrawal. All the positives vanished on repeat testing as the rashes cleared.

Elevated serum NO levels are seen in patients with septic shock syndrome, rheumatoid arthritis and in the cerebral spinal fluid of neurological trauma patients [69–71]. Recently, elevations were noted in animals with uveitis and in patients with Behcet's syndrome who had active lesions in the skin or in the eye [72,73]. Endothelial dysfunction may play a central pathological role in the aforementioned diseases as well as in corticosteroid addicted patients. The continuous and intermittent nature of elevations of the NO in our patients remains unexplained.

Since the withdrawal phase of these corticosteroid-addicted patients can last for over a year, NO levels can be employed to help gauge recovery time and possibly determine when the withdrawal will be complete. It is suggested that elevated levels can be used as a diagnostic test to aid in the diagnosis of steroid addiction

as opposed to eczema. Recognition of steroid addiction is important, since therapy is different to that given to topical eczema patients. Recent reports suggest that treating these 'chronic' eczema patients with topical immunomodulators, oral immunosuppressives and antimetabolic agents would be of great assistance in controlling their disease [74–83]. We believe that these 'chronic' eczema patients are in reality corticosteroid addicted and should not be exposed to more potentially problematic therapies. We have experienced minimal, if any, success with the topical immunomodulators. As shown by NO levels, these patients are entirely different and should be managed as such [84]. It is suggested that usage of as yet unknown NO inhibitors might help alleviate the flares of erythema in corticosteroid-addicted patients.

The corticosteroid-addicted patients are exceptionally common and are seen throughout the world. Consideration for this diagnosis should be made when a longstanding chronic expanding eczematous rash worsens despite 'good dermatological care' with corticosteroids.

Expert commentary

For the last 50 years the standard treatment for the chronic eczematous patient has been the usage of topical and systemic corticosteroids. More problematic cases and more severe,

Box 10. Corticosteroid addiction: unusual situations seen.

- Surgeon with a hand dermatitis – repeated evaluations for latex allergy
- Air bag dermatitis face – treated for 3 years
- Nurses or spouses of MDs – availability of steroid preparations
- Unreported ophthalmic steroid usage and then steroid cream for eyelid rash years later
- Suicidal – owing to continual fierce burning skin – several patients
- Allergist/dermatologist/internist all treating patients at the same time with different steroids
- Holistic MDs, chiropractors and herbalists are visited by patients
- Language barriers – Farsi, Russian, Korean, Japanese and Chinese patients – must have translator to fully explain at each visit
- Legal actions – 6 cases
- Mother–daughter; husband–wife: both with addiction
- Breast implants removed – nipple dermatitis in an atopic
- Workman's compensation – factitial and malingering suspected
- Internet visited by patients – several being advised by e-mail only

Table 1. Nitric oxide study.

Group	Median	Mean	SD
Addicted group	2.2	2.96	2.86
Cured group	1.3	1.30	0.78
Eczema group	1.5	1.40	0.93

symptomatic eczema patients are being seen worldwide. The natural history of eczema usually features pruritis, rash and excoriations in youth with a diminution of symptomology and a clearing of eczema in most patients as they approach adulthood. In the past, the adult eczema patient usually exhibited only minimal rash in small areas of the body. It is suggested therefore that the various ‘difficult’ cases of eczema now being seen in a myriad of patients is due to the over usage and continual usage of topical and systemic corticosteroids. From a simple mild eczematous patch, these rashes evolve into full-blown generalized eruptions that are then managed with antimitotic and immunosuppressive medications in addition to the steroids, further exposing the patients to the possibility of worse side effects and problems. These patients would be cured if it was recognized that the rash and redness is corticosteroid dependant and not eczema. Total cure lies in absolute withdrawal of corticosteroids with the completion of the process taking 6–24 months.

Five-year view

Results of allergy testing in ‘eczema’ patients rarely aids in diagnosis and will be performed less frequently. As physicians become more comfortable in managing the stormy steroid withdrawal phases of ‘chronic eczema’ patients they will confidently continue to withhold corticosteroids. They will also more cautiously use immunocompromising drugs that exhibit more severe side effects. Patients will benefit. The internet has allowed patients to access more information and, now being more proactive, have begun in earnest to question the usage of corticosteroids for their problem. Finally, the recognition that NO is probably the mediating chemical factor in this steroid addiction will stimulate more research and studies. This chemical factor will also be examined in other diseases associated with erythema. The development of anti-NO medications will be developed for use in various skin

Table 2. Nitrate levels – normal 0.25–2.8 µg/ml.

1st quarter (µg)	2nd quarter (µg)	3rd quarter (µg)	4th quarter (µg)
<i>Case 1: 54-year-old male</i>			
4.7	4.3	3.4	2.8
6.2	5.9	5.1	4.0
5.3	5.2		2.2
<i>Case 2: 72-year-old female</i>			
6.7	2.9	1.3	1.5
2.0	2.9		

antimitotics in these patients will lessen and will be re-evaluated. The topical immunomodulators tacrolimus and pimecrolimus will be used less frequently because both short- and long-term benefits are lacking.

Key issues

- Patients with worsening eczematous rashes being treated with larger amounts of topical and systemic corticosteroids should be considered addicted to this medication as the sole cause of the worsening rash.
- Patients are usually atopics and the problem starts as a small area of eczema. Allergens, dust mites and sun exposure are not etiological factors.
- The skin burns severely and pruritus is minimal.
- Patch testing and internal medicine evaluations are usually within normal limits.
- A spongiotic dermatitis is the pathology on skin biopsy.
- The skin redness and eczematous changes is based on elevation of serum nitric oxide, not flares of atopic dermatitis.
- Withdrawal from the corticosteroids typically leads to total cure but can take from 6 to 24 months for complete resolution.

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Affiliations

- *Marvin J Rapaport, MD*
Clinical Professor of Dermatology, UCLA, 436 No. Bedford Drive, Suite 306, Beverly Hills, CA 90210, USA
Tel.: +1 310 274 4401
Fax: +1 310 274 5194
rapndad@aol.com
- *Vicki Rapaport, MD*
UCLA, 436 No. Bedford Drive, Suite 306, Beverly Hills, CA 90210, USA
Tel.: +1 310 274 4401
Fax: +1 310 274 5194