

dismal survival curve that characterizes most patients with Hallopeau-Siemens disease. Based on the encouraging data generated by Wagner and colleagues,<sup>1</sup> I would urge pursuit of a similar study addressing the potential efficacy and surgical practicality of sentinel node biopsy in inherited EB. Were a benefit identified, then this would be the first major clinical advance in the care of adults with EB in at least many decades.

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The author has no relevant financial interest in this letter.

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## VIGNETTES

### Serum Nitric Oxide Levels in "Red" Patients: Separating Corticosteroid-Addicted Patients From Those With Chronic Eczema

When atopic dermatitis worsens, with a spreading eruption accompanied by erythema and a burning sensation, treatment often includes superpotent topical corticosteroids, systemic corticosteroids, or both topical and systemic immunosuppressive agents. Because of our past evaluations of patients with these symptoms,<sup>1</sup> we believe that they do not reflect worsening eczema, but that the redness and burning sensation are due to continuous vasodilation, which often is accompanied by intercellular and extracellular edema. Since nitric oxide is synthesized by the endothelium of the vasculature and functions as a vasodilator,<sup>2</sup> this might explain vasodilation and redness in corticosteroid-addicted patients.

Serum nitric oxide levels were measured by the Griess reaction.<sup>3</sup> Nitric oxide measurement is difficult because of its brief half-life. Therefore, nitrate and nitrite levels, which are stable end products of nitric oxide metabolism, were used as markers. Normal serum values are 0.25 to 2.8 mg/mL for nitrates and 0.06 to 0.6 mg/mL for nitrites.

The addicted group, 38 consecutive corticosteroid-addicted patients, ceased corticosteroid use on their first visit, when their serum nitric oxide level was measured. The cured group consisted of 26 previously addicted patients who were called to the office to also have their serum nitric oxide level measured; they had not had a recurrence of any eruption for at least 1 year. Lastly, the eczema group, 20 patients with untreated and very mild eczema (mild eyelid dermatitis or a few nummular patches

### Blood Serum Levels of Nitrates as Markers of Nitric Oxide in Corticosteroid-Addicted Patients, Cured Patients, and Patients With Eczema

Group	Nitrates, mg/mL		P Value
	Median	Mean (SD)	
Addicted (n = 38)	2.2	2.96 (2.86)	<.001
Cured (n = 26)	1.3	1.30 (0.78)	
With eczema (n = 20)	1.5	1.40 (0.93)	

on their body), had their serum nitric oxide level measured at their first visit.

In the addicted group, between 2 and 10 blood specimens were taken from each patient; and of 144 specimens analyzed, 70 (20 patients) had elevated nitrate levels. Of the 18 patients who had normal results, 13 only had atrophic corticosteroid-addicted skin and minimal, if any, erythema. In the cured group, 1 to 4 specimens were taken from each patient; of 42 specimens analyzed, 3 (2 patients) had elevated nitrate levels. In the eczema group, 1 to 3 specimens were taken from each patient; of 29 specimens analyzed, 5 (4 patients) had elevated values. The evidence was strong that the addicted group had higher mean nitrate levels than the cured and eczema groups ( $P < .001$ ) (Table). There was additional evidence that the "red" addicted patients had higher mean nitrate levels than the nonred, addicted patients.

Multiple nitrate levels were measured in the addicted patients as they pursued their withdrawal and became less erythematous. Corticosteroid clearance took several months in most patients and the nitric oxide levels became normal after they experienced their last flare.

Elevated serum nitric oxide levels are seen in patients with septic shock syndrome, Behçet syndrome with or without active lesions, or rheumatoid arthritis, and in the cerebral spinal fluid of patients with neurological trauma.<sup>4</sup> Endothelial dysfunction may play a central pathological role in the aforementioned diseases as well as in corticosteroid-addicted patients. Since the withdrawal phase of these addicted patients can last for a year or more, nitric oxide levels can be used to gauge recovery time and to determine when the withdrawal will be complete and the dermatitis and erythema cease. Recognition of corticosteroid-addicted patients with elevated nitric oxide levels is important since therapy will not be the same for them and for patients with pure eczema. These addicted patients are represented in the red face syndrome, postlaser/peel syndrome, status cosmeticus, red scrotum syndrome, perianal atrophoderma, vulvodynia, chronic actinic dermatitis, and chronic recalcitrant eczema.<sup>5</sup> In our experience, the use of immunomodulating, oral immunosuppressing, and antimitotic agents does not help these chronically red corticosteroid-addicted patients.<sup>6</sup> We believe that the rash does not represent eczema anymore, but permanent vasodilatation caused by elevated serum levels of nitric oxide. The usage of nitric oxide inhibitors should be studied during flares of erythema.

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The authors have no relevant financial interest in this article.

The statistical analysis was performed by Jason Lenderman and Robert Gould, PhD, of the UCLA Department of Statistics, Los Angeles, Calif. The nitrate/nitrite assays were performed under the direction of John DiGregorio, MD, of National Medical Services Laboratory, Willow Grove, Pa.

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### Alcohol-Induced Application Site Erythema After Topical Immunomodulator Use and Its Inhibition by Aspirin

The topical immunomodulators tacrolimus and pimecrolimus have proven effective in managing atopic dermatitis.<sup>1,2</sup> Reported adverse effects are infrequent and most often consist of transient burning, warmth, or erythema at the application site upon initial use.<sup>1,2</sup> We recently identified 3 patients who experienced application site erythema following the consumption of alcohol after using topical tacrolimus or pimecrolimus for the treatment of facial dermatoses. While this reaction has sometimes been mentioned for topical tacrolimus,<sup>3</sup> there are no reports in the literature of this effect occurring with topical pimecrolimus. To study potential ways of alleviating this unwanted response, we conducted a double-blind controlled evaluation of 2 of the 3 patients after blocking 2 important mediators of vasodilatation, histamine and prostaglandins.

**Methods.** On days 1 through 12, participants applied 4 randomly coded preparations (0.1% tacrolimus oint-

ment, 1.0% pimecrolimus cream, a control ointment, and a control cream) twice daily to 4 designated locations on the face and 4 designated locations on the forearms. Challenges with 240 mL (8 oz) of red (participant 1) or white wine (participant 2) were conducted on day 0 and after the second daily application on days 3, 6, 9, and 12, and participants subjectively evaluated the extent (none, mild, moderate, or severe) of any erythema (**Table**). Oral acetylsalicylic acid, 325 mg, was taken twice daily from days 4 through 6, and histamine blockers oral cetirizine, 10 mg once daily, and cimetidine, 400 mg twice daily, were taken on days 10 through 12.

**Results.** At baseline, both participants consumed alcohol without experiencing flushing. After 3 days of applications twice daily, both participants experienced moderate to severe facial flushing 5 to 10 minutes following alcohol consumption. It was limited to the areas of tacrolimus and pimecrolimus application (**Figure, A**), as there was no flushing at control sites. The intensity of the erythema was sharply reduced after the addition of oral aspirin for 3 days (**Figure, B**). Following a 3-day washout period when no medication was taken orally, 1 participant again experienced facial flushing at both immunomodulator sites after alcohol consumption, and the erythema worsened after oral intake of histamine 1 and histamine 2 blockers for the subsequent 3 days. In the second participant, no facial erythema occurred with alcohol consumption after the 3-day washout period, while mild flushing occurred only at the site of tacrolimus application after the subsequent 2 days of antihistamine use. The duration of flushing was approximately 1 hour in all instances. Of note, the 3-day washout period may not have been sufficient to clear all of the effects of aspirin, as the flushing response at day 9 was diminished compared with what it was on day 3 in both participants. Both participants also reported warmth at the site of facial erythema with each episode.

**Comment.** Generalized facial flushing following alcohol consumption is known to result from the accumulation of acetaldehyde following a block in alcohol metabolism, commonly at the level of the enzyme aldehyde dehydrogenase.<sup>4</sup> Inherited mutations in aldehyde dehydrogenase alleles, as well as many oral medications, have been shown to inhibit the breakdown of acetaldehyde.

Day, No. †	Participant 1				Participant 2			
	Pimecrolimus Cream	Tacrolimus Ointment	Control Cream	Control Ointment	Pimecrolimus	Tacrolimus	Control Cream	Control Ointment
0	0	0	0	0	0	0	0	0
3	++	++	0	0	+++	+++	0	0
6	0	0	0	0	+	+	0	0
9	0	0	0	0	++	++	0	0
12	0	+	0	+‡	+++	+++	0	0

\*Neither participant noticed erythema on the forearm sites of application at any time; key to degree of erythema: 0 = none; + = mild; ++ = moderate; and +++ = severe.

†Aspirin was taken on days 4, 5, and 6.

‡With the exception of 1 incident of mild erythema, perhaps from the inadvertent spread of tacrolimus onto that site, no erythema was observed on areas of control cream or ointment application.