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Clinical Therapeutics for Atopic Dermatitis and Fungal Infections: An Update

Topical Steroids in Pediatric Atopic Dermatitis

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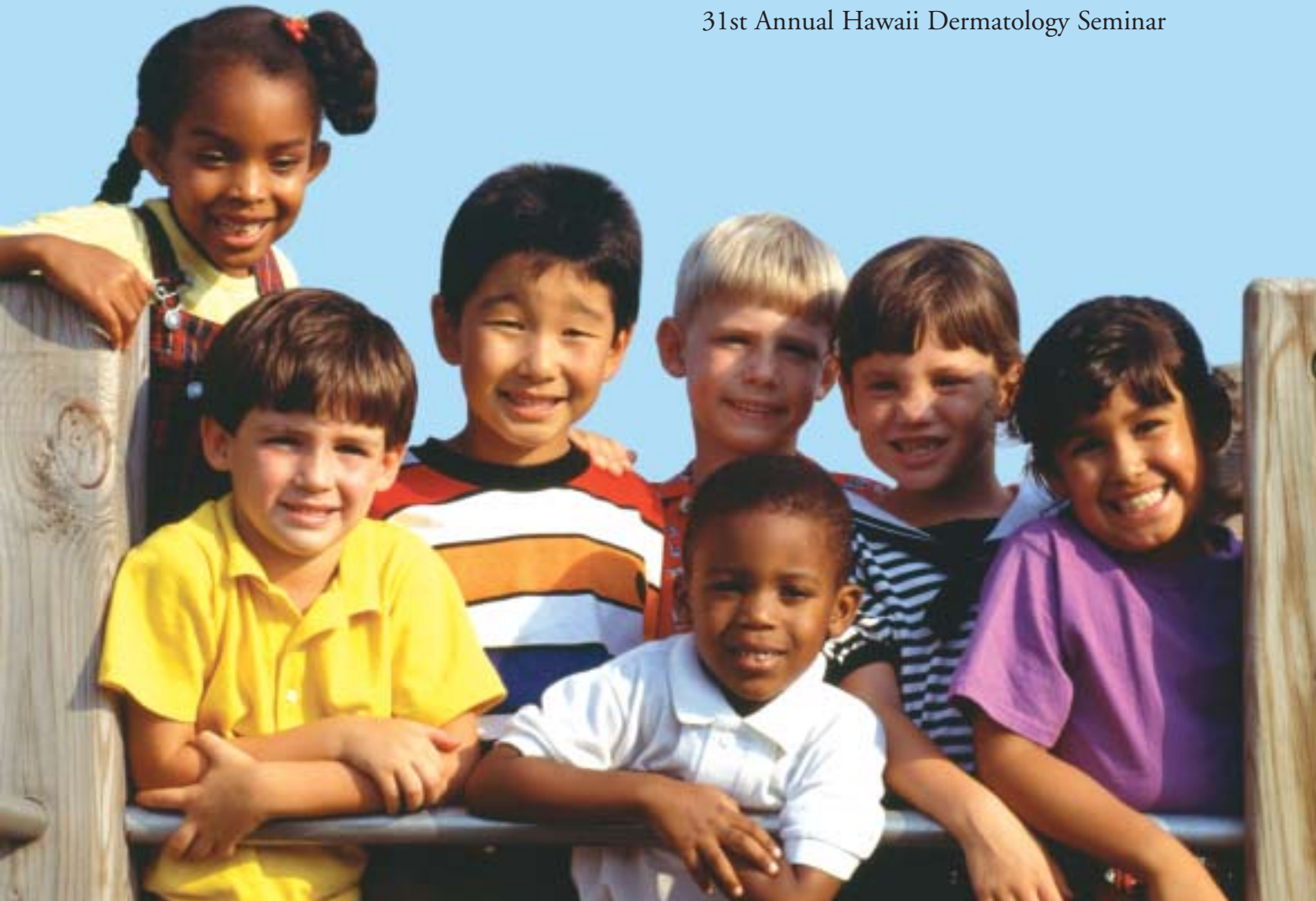

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TARGET AUDIENCE

This activity is intended for health care professionals, including dermatologists and pediatricians, who are involved in the treatment of patients with atopic dermatitis.

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Topical Steroids in Pediatric Atopic Dermatitis

Leon H. Kircik, MD

Recent epidemiologic data show that more than 15 million individuals in the United States have atopic dermatitis (AD).[1] In the majority of patients, AD peaks in the first years of life[2,3]; almost 50% of patients with AD are 12 years of age or younger.[4] An estimated 40% continue to experience AD symptoms into adulthood.[2]

The data also show a trend toward an increasing prevalence of AD in children. The environmental changes may contribute qualitatively or quantitatively to antigen exposures, which can trigger the disease.

The High Costs of AD

Direct costs include payments for over-the-counter treatments and therapies that are not covered by insurance (for example, allergy testing and alternative therapies). However, most of the financial burden of AD results from indirect costs.[1,5] These include losses to employers of parents of children with AD; for example, if a child cannot go to school, a parent may not be able to go to work. Lost productivity attributed to AD is estimated at $619 million yearly, including $183 million in lost workdays. Since AD primarily affects children, the majority of productivity losses is due to caregiver lost workdays, amounting to $249 million. The remaining $188 million is attributable to restricted activity days due to AD.

In addition to monetary costs, AD substantially affects quality of life (QOL). QOL issues include itching, sleeplessness, poor work functioning, and decreased coping skills at work and at home.[5]

Goals and Options for Treatment in Children

There are four recognized objectives for the treatment of AD in children (summarized in **Table 1**): education, induction of remission, maintenance, and rescue of flares.[2,6]

EDUCATION

Parents and older children must understand the value of emollients (as discussed below under "Maintenance Therapy") and should know the proper techniques for bathing and emollient application.

In addition, parents and patients should be informed about allergens. It is advisable to avoid known or suspected allergens, despite the fact that allergen avoidance currently has no established role in the management of patients with AD.[7] An evidence-based review of food allergy and dust-mite avoidance strategies for established AD failed to demonstrate the therapeutic value of food avoidance (except, perhaps, the avoidance of eggs in infants).[7] Tan and colleagues[8] conducted a study of house-dust–mite reduction measures and concluded that these measures may benefit children with AD, but other studies have failed to produce definitive evidence that reducing dust mites can improve AD.[7,9]

INDUCTION OF REMISSION

The use of topical corticosteroids have long been recognized as key elements in regimens designed to induce remission of AD. Topical corticosteroids are discussed in detail in the following section.

In addition to these measures, patients should be monitored for skin infections and appropriate antimicrobial therapy should be used as indicated. In particular, it is important to recognize the role of *Staphylococcus aureus* in disease flares. *S. aureus* colonizes the skin of most patients with AD. Topical antibiotics and anti-inflammatory therapy usually are effective for limited infections. Patients with widespread infections or severe flares often respond to oral antibiotics.

The use of longer courses of oral antibiotics is not recommended because of the increased prevalence of methicillin-resistant strains of *S. aureus*. Bacterial cultures and surveillance of family members are advisable prior to treatment of patients with recurrent infections so that the appropriate antimicrobial therapy and environmental protection strategies can be implemented.

MAINTENANCE THERAPY

Emollients have long been recognized as, and remain the foundation for, effective maintenance therapy and the prevention of relapse. The purpose of emollient applications is the optimization of skin barrier function. In general, emollient formulations with greater concentrations of lipids provide a more effective barrier than water-based products. In fact, some recent studies have explored the possible benefits of including stratum corneum lipids in emollients. The results of one uncontrolled study, using an emollient containing the stratum corneum lipid ceramide, showed benefit over routine emollient therapy.[10]

Topical corticosteroids are the cornerstone for acute control of flares, but have not been considered safe for long-term maintenance. However, intermittent therapy—for example, twice-weekly applica-

Table 1. Objectives for Treating AD in Children

Education: importance of emollients and avoidance of triggers
Induction of remission: topical corticosteroids, treatment of infection as needed
Maintenance: barrier creams, emollients, topical corticosteroids twice weekly, topical calcineurin inhibitors
Rescue of flares: topical corticosteroids ultraviolet light, methotrexate, cyclosporine

AD = atopic dermatitis. **Source:** Courtesy of Leon H. Kircik, MD

tions—with midpotency topical agents may help prevent recurrence of AD flares without causing the adverse effects commonly seen with chronic use of corticosteroids.[11,12]

Topical calcineurin inhibitors have been shown to be safe and effective for long-term maintenance in children with AD. In one 4-year study of tacrolimus, Hanifin and colleagues[13] reported that use of this agent was safe and effective in children with moderate and severe AD. A 1-year study of pimecrolimus by Wahn et al[14] demonstrated that chronic use of this agent reduced both the number of flares and the amount of corticosteroids required when treatment was initiated at the first signs or symptoms of AD activity.

Other investigators have suggested that the combined, intermittent use of topical corticosteroids (twice weekly) and a topical calcineurin inhibitor (5 days/week) may be helpful for patients with severe disease.[15,16]

Of course, all dermatologists who treat AD and many parents are aware of the US Food and Drug Adminisration (FDA) Public Health Advisory regarding topical calcineurin inhibitors that was published in 2005 and led to the "black box" warning in the labeling of these agents. Thorough discussions of this issue have occurred at professional meetings over the last several years and in numerous articles in the dermatology literature. It seems to be the consensus of experts that the systemic absorption of topical calcineurin inhibitors is minimal.

RESCUE OF FLARES

Aggressive treatment is indicated for flares, and the strategy is the same as that for inducing remission. In addition, whenever possible, the underlying trigger for a flare should be determined. These include bacterial or viral infections, dry skin, psychological stress, and noncompliance with maintenance therapy.[6]

The benefits of phototherapy in the control of AD are well recognized. Modalities include treatment with ultraviolet A (UVA), UVB, and psoralen with UVA light (PUVA). Narrow-band UVB phototherapy is preferred by many for maintenance therapy in patients with moderate-to-severe disease that does not respond to maintenance treatment with topical agents.

The use of oral corticosteroids is indicated when intensive treatment with topical agents fails. When a flare cannot be controlled with topical corticosteroids and phototherapy, oral cyclosporine may be considered in patients in whom its use is not contraindicated. (The reader is referred to Akhavan and Rudikoff[17] for a discussion of clinical guidelines for the use of cyclosporine in AD.)

Other systemic therapies that have been used to manage AD flares include azathioprine, mycophenolate mofetil, methotrexate, and interferon-α.[18] Efficacy studies have provided support for the use of these agents in appropriate circumstances.[18] However, no evidence has been published supporting the use of antihistamines and leukotriene inhibitors in AD, although these are commonly and widely used for such therapy. Antihistamines with sedative effects may be useful during a flare, not because of any effects of AD symptoms, but mild sedation may help patients (and their caregivers) sleep better.

Pediatric Use of Corticosteroids: Special Considerations

Nelson and colleagues[19] conducted a study to attempt to determine appropriate topical corticosteroid dosages for pediatric patients. The researchers point out that standards for the quantity of topical agent to be applied have not been well established. In clinical trials of these topical agents, investigators often specify quantities that should be applied in terms such as "a thin layer" or "a layer just sufficient to cover the entire affected area." This has the potential for causing variability in results among individuals in the clinical trials and also in results seen in individuals in clinical use. Nelson's group also states that the "rule of 9s" to estimate the amount of topical agent needed for adequate coverage of body surface area (BSA) provides a good estimate for adults, but not for children.

Instead, Nelson et al[19] developed guidelines for the quantity of medication needed for total body application based on a child's age, height, and weight. **Table 2** shows an example of the use of their method. In this example, the researchers show the amount of topical corticosteroid that must be applied, per body part, twice daily for 1 month to achieve a concentration of 2.0 mg/cm^2.

Several new products have been introduced that are approved by the FDA for pediatric indications, even in very young children. One is a foam formulation of desonide, which is approved for children down to 3 months of age. Although hypothalamic-pituitary-adrenal (HPA)-axis suppression is seen with this agent,

Table 2. Topical Corticosteroid Needed to Achieve a Concentration of 2.0 mg/cm^2*

Age	Total Body	Hands	Feet	Each Leg	Each Arm	Chest	Back	Face	Scalp	Groin & Buttocks
6 months	0.5 kg	25 g	35 g	50 g	35 g	60 g	60 g	45 g	45 g	30 g
6 years	1 kg	50 g	70 g	140 g	70 g	130 g	130 g	65 g	65 g	60 g
12 years	1.6 kg	80 g	110 g	230 g	110 g	200 g	200 g	90 g	90 g	100 g
Adult	2.3 kg	120 g	160 g	375 g	160 g	300 g	300 g	80 g	80 g	135 g

*Applied twice daily for 1 month.
Source: Nelson AA, Miller AD, Khanna V, Fleisher AB, Balkrishnan R, Feldman SR. How much of a topical agent should be prescribed for children of different sizes? Poster presented at: 65th Annual Meeting of the American Academy of Dermatology; February 2-6, 2007; Washington, DC. Abstract P721. Reprinted with permission.

HPA-axis function returns to normal when use of the drug is discontinued. Desonide hydrogel is another formulation of this drug, which also has FDA approval for use in children down to 3 months of age. HPA-axis suppression was shown in one out of 37 patients in a clinical trial. (Although the labeling states an association with HPA-axis suppression, it may be that this finding actually was the result of a technical problem the investigators had in drawing blood from this one patient.)

Another newly approved agent, a 0.05% lotion formulation of fluticasone propionate, is indicated for once-daily application for patients down to 1 year of age and is not associated with HPA-axis suppression. Eichenfield and colleagues[20] conducted two separate but parallel randomized, double-blind, placebo-controlled studies. A total of 438 subjects with moderate to severe disease participated, ranging in age from 3 months to 16 years. (The demographics and other characteristics were similar in the two studies, referred to as Study A and Study B.)

Weekly assessments were made of the patients' head and neck, trunk, arms, and legs. For each body site, the investigators estimated the BSA affected and assessed the severity of five key signs and symptoms: erythema, scaling, infiltration/papulation, erosion/oozing/crusting, and pruritus. A physician's global assessment (PGA) scale was used to score changes in severity of these five signs and symptoms from baseline to the end of the 4 weeks of treatment.

The primary end points that determined overall treatment success were ≥50% clearance of lesions plus improvement or no change in ≥75% of the 20 symptom assessments on PGA. Primary end points on additional analysis (ie, not planned analysis) were ≥50% clearance of lesions plus improvement or no change in 100% of the 20 symptom assessments; the findings from the planned analysis were confirmed by those of the additional analysis. The secondary end points were ≥50% clearance of lesions on PGA and the subjects' or parents' assessment of response to treatment.[21]

In Study A, ≥50% clearance of lesions on PGA was significantly higher with fluticasone propionate lotion (n=83) than with vehicle (n=35) (P<0.001). In Study B, the PGA of ≥50% lesional clearance was significantly higher with fluticasone propionate lotion (n=73) than with vehicle (n=29) (P<0.001). Subjective assessments by the subjects/parents in Study A indicated that 50% in the active treatment group rated their response as excellent, compared with 15% who used vehicle only (P<0.001). The differences in Study B were similar and also statistically significant: excellent responses were reported by 48% of patients who received fluticasone, compared with 7% of the patients who received vehicle (P<0.001).

The most common adverse effects were burning and stinging, reported by 4% of patients who received fluticasone and 5% of subjects in the control group. The lack of difference between the two groups is not surprising; many patients with AD have burning and stinging in response to the application of almost any topical agent.

This formulation has a cosmetically acceptable, emollient-rich vehicle that spreads easily, even in hair-bearing areas.

Summary

AD remains one of the most common diseases seen in dermatologists' offices. Improvements continue to be made in topical corticosteroids, particularly those tested specifically in pediatric populations; examples are the new formulations of desonide (in foam and hydrogel vehicles) and of fluticasone propionate (a lotion vehicle). These new agents are FDA-approved and appropriate for use in children.

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Topical Antifungals: An Update

Douglas W. Kress, MD

The species of fungi that infect the skin in humans—that is, the dermatophytes—are yeasts and the fungi imperfecti (also called deuteromycota), including epidermophytons, microspora, and trichophytons. The incidence and characterization of dermatophytic infections in the United States have been difficult to estimate because data are available only on patients who seek treatment for their conditions. A casual survey of pharmacy shelves reveals a large number of over-the-counter topical antifungal medications available for self-treatment by patients with a variety of dermatophytic infections (in most cases, self-diagnosed). Unless these infections persist or become more severe, self-treating patients are not likely to seek professional medical help.

Gupta and Cooper[1] conducted a statistical study of the incidence of dermatophytic infections in the United States, analyzing data from the National Ambulatory Medical Care Survey (1990-1999). According to their report, dermatophytic infection of the body (tinea corporis) was the most common primary diagnosis (22%), followed by onychomycosis (19%), tinea pedis (12%), and tinea cruris (10%); in 16% of cases, the site of infection was not specified. The investigators also note that, in many cases, the primary diagnosis was accompanied by secondary and even tertiary diagnoses of fungal infections on other parts of the body.

Based on their findings, Gupta and Cooper note that for most of these infections, topical agents are the first-line therapy (exceptions are onychomycosis, tinea capitis, and the deep mycoses). In addition, they conclude that, given the frequent occurrence of multiple concomitant infections, a wide-spectrum agent is preferable, ideally one that is active against *Malassezia* species as well as dermatophytes that cause tinea infections.

Topical Antifungal Agents: A Review

A large number of agents are available to treat cutaneous fungal infections (**Table**). Amphotericins and nystatin were the first antifungals developed; in 1959, amphotericin was the first antifungal agent approved by the US Food and Drug Administration (FDA). Within a few years, griseofulvin and miconazole (the first in a line of agents classified as azoles) became available. Naftifine and terbinafine (both allylamines) and the benzylamine agent butenafine were FDA approved in 1988, 1992, and 2001, respectively. Most recently, in 2004, the FDA approved ciclopirox olamine, the first antifungal in a new class called hydroxypyridones.

Table. Topical Antifungals Available in the United States

	Class	Generic	FDA Approval
2000s >	Hydroxypyridone	Ciclopirox olamine	2004
1980s >	Amines: allyl/benzyl	Terbinafine	1992
		Butenafine	2001
		Naftifine	1988
1970s >	Azoles	Econazole	1982
		Ketoconazole	1985
		Clotrimazole	1993
		Sertaconazole	2003
		Oxiconazole	1988
		Miconazole	1974
1950s >	Polyenes	Nystatin	1976
		Amphotericin B	
	Others	Selenium sulfide	1975
		Sulfacetamide	
		Tolnaftate	
		Undecylenic acid	

Source: Courtesy of Douglas W. Kress, MD, and Shay Jones, PA-C, MEd, MPH

INDICATIONS AND MECHANISMS OF ACTION

Amphotericin B is not approved as a topical agent and is rarely used in the United States. Nystatin, also in the polyene class, is approved for the treatment of yeast infections caused by *Candida* species. Nystatin is fungicidal and also has fungistatic activity, binding to ergosterol in the cell wall, causing leakage.

The azole class of antifungals, which are widely used, have a very broad spectrum of action, with approximately equal efficacy against both yeast and dermatophytes. These agents are also fungistatic, but, in contrast to nystatin, the azoles work by blocking the synthesis of ergosterol in the cell wall. In addition, oxiconazole–an imidazole agent within the azole class–has been shown to be fungicidal as well as fungistatic.

Allylamines and benzylamines inhibit the synthesis of ergosterol. These agents are fungicidal and highly effective against dermatophyte infections and are fungistatic against *Candida*.

Like oxiconazole, the hydroxypyridone ciclopirox is both fungicidal and fungistatic, with potent activity against both yeast and dermatophytes. Ciclopirox interferes with active membrane transport and inhibits prostaglandin and leukotriene synthesis.

NOTES ON INDIVIDUAL AGENTS

This section highlights some information regarding individual topical antifungal agents that may be helpful in choosing among these agents for specific clinical situations.

As noted above, all of the agents in the azole class are effective against tinea infections, candidiasis, and *Malassezia furfur*, the cause of tinea (pityriasis) versicolor. In addition, at least one study has shown that econazole has antibacterial activity. Kates and colleagues[2] compared econazole with vehicle in the treatment of a small group of patients who had bacterial infections of interdigital web spaces, with no evidence of concomitant dermatophytic infection. The infections cleared completely in 88% of patients in the econazole group; none of the patients in the vehicle group had clearance of their infections.

Miconazole also has demonstrated activity against some gram-positive bacterial species.[3] Other agents in the azole class also may have antibacterial activity, but such studies have been reported only on econazole and miconazole.

Oxiconazole is rapidly absorbed into the stratum corneum and, therefore, is effective—and FDA approved—for once-daily use. Efficacy of once-daily dosing was demonstrated by Ellis and colleagues,[4] who compared oxiconazole cream with placebo in both once- and twice-daily regimens in a group of patients with tinea pedis. The cure rates were similar in both active-treatment groups: 80% in the patients who used the drug once a day and 75% who applied oxiconazole twice daily.

More recently, Gupta[5] conducted an overview of the clinical trials that confirmed the efficacy of oxiconazole used once or twice daily, assessed in terms of both mycologic cure and clinical response.

In 2000, Crawford and colleagues[6] published a systematic review of the evidence published to date on topical antifungals for tinea infections of the skin and nails of the foot. According to the summary of evidence, efficacy of the azoles is strongly related to the duration of treatment. For example, the cure rate with clotrimazole after 1 week of therapy was 35%, but after 4 weeks, the cure rate was 70%.

As a class of agents, the allylamines/benzylamines are dramatically more effective as a class of agents for treating dermatophytic infections than for treating yeast infections[7]; for treating the latter, one of the azole antifungals is preferable. One agent in this class, butenafine, is now available as an over-the-counter medication.

Ciclopirox is available in lotion, cream, shampoo, and nail lacquer formulations. The nail lacquer is associated with a cure rate for onychomycosis of only 8% to 12%.[8] In terms of cure, oral therapy with terbinafine yields much higher cure rates, defined as 59% mycologic cure plus new, unaffected nail growth measuring at least 5 mm.[9] However, oral terbinafine—although not contraindicated in pediatric patients—has not been studied to determine the safety or efficacy of this agent for onychomycosis in the pediatric population. Therefore, ciclopirox lacquer may be a better choice for young patients.

Conclusion

Superficial fungal infections caused primarily by *Trichophyton* species, *Microsporum* species, *Epidermaphyton floccosum*, and *M. furfur* are the most commonly diagnosed skin diseases in the United States. Fortunately, several classes of topical antifungal agents are widely available to safely and effectively treat these infections. Most of these are broad-spectrum antifungals and are active against all of these organisms. Variations exist in demonstrated activity against specific dermatophytes. The choice of individual agents should be based on antifungal activity against the causative organisms (when this is an issue) and on factors that may affect compliance in individual patients.

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