

Beyond JAAD July 2019: Articles of interest to dermatologists from the nondermatologic literature



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CONTACT DERMATITIS AND SENSITIZATION IN PROFESSIONAL MUSICIANS

From a group of >200,000 patients with a history of dermatitis, the authors identified 236 patients who were professional musicians. Compared with the control group of dermatitis patients who were not musicians, the patients who were musicians were more frequently male (58.6%) and of younger age (60.6% <40 years). The musicians more frequently had facial dermatitis than the control group (23.7% vs 15.7%, respectively) and less often had leg dermatitis (musicians 5.1% vs controls 10.7%). In the string section (violin, viola, cello, double bass, guitar), irritant dermatitis included fiddler neck, cellist chest, and guitar nipple. Common allergens included colophonium (resin), exotic woods, and metals (nickel, cobalt, and chromium). Other associated skin diseases included paronychia and callosities. In the woodwind section (flute, oboe, clarinet, bassoon, saxophone), irritant dermatitis included irritant cheilitis and flautist chin. Common allergens included exotic woods and cane reed. A commonly associated skin condition was herpes labialis. In the brass section (trumpet, trombone, horn, tuba), irritant dermatitis included horn player lip and metal allergies, and an associated skin condition was again herpes labialis. The authors cite previous studies showing that the percentage of musicians with professionally linked skin conditions varies from as low as 20% to as high as 50%.

Kraft M, Schubert S, Geier J, Worm M. Contact dermatitis and sensitization in professional musicians. *Contact Dermatitis*. 2019;80:273-278.

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PROBIOTICS IN LATE INFANCY REDUCE THE INCIDENCE OF ATOPIC DERMATITIS: A RANDOMIZED CONTROLLED TRIAL

The role of the microbiome in health and disease continues to garner attention. Probiotics have long been used as both treatment and prevention of eczema without a solid evidence base. Schmidt et al have added a double-blinded placebo-controlled trial to the body of literature. In total, 144 infants received a daily mixture of probiotic strains for a 6-month study period starting at a mean age of 10.1 months. Infants in the probiotic group had a 4.2% incidence of atopic dermatitis compared with 11.5% in the control group. There were no differences noted in the incidence of other atopic comorbidities, including food reactions, asthma, or rhinitis. It should be noted that the study was partially funded by the probiotic manufacturer.

Schmidt R, Pilmann Laursen R, Bruun S, et al. Probiotics in late infancy reduce the incidence of atopic dermatitis: a randomized controlled trial. *Pediatr Allergy Immunol*. 2019;1-6.

COMPARISON OF EFFICACY OF AMINOLAEVULINIC ACID PHOTODYNAMIC THERAPY VS. ADAPALENE GEL PLUS ORAL DOXYCYCLINE FOR TREATMENT OF MODERATE ACNE VULGARIS-A SIMPLE, BLIND, RANDOMIZED, AND CONTROLLED TRIAL

The authors undertook a randomized, controlled trial involving 46 patients with moderately inflammatory facial acne. Group A (23 patients) received 2

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sessions of photodynamic therapy (using a red-light source) separated by 2 weeks, and group B (23 patients) received doxycycline 100 mg/day plus adapalene gel 0.1%. Starting at the sixth week, both groups used adapalene gel 0.1% as maintenance therapy until 12 weeks of follow-up. The median percent reduction in noninflammatory lesion count and total lesion counts at 6 weeks was found to be significantly higher in group A; noninflammatory lesions decreased by 55% in group A and 41% in group B. Inflammatory lesions followed a similar trend, with a 61% decrease in group A and 58% decrease in group B. At 12 weeks, inflammatory lesion counts were more reduced in group A (84%) than group B (74%), and the noninflammatory lesion count was reduced 55% in group A and 41% in group B. Total lesion counts at 12 weeks decreased by 79% in group A and 67% in group B. The authors conclude that aminolaevulinic acid photodynamic therapy offers promise as an alternative treatment for moderately severe inflammatory acne vulgaris and that it is more effective than a combination of doxycycline and adapalene gel.

Nicklas C, Rubio R, Cardenas C, Hasson A. Comparison of efficacy of aminolaevulinic acid photodynamic therapy vs. adapalene gel plus oral doxycycline for treatment of moderate acne vulgaris—a simple, blind, randomized, and controlled trial. *Photodermatol Photoimmunol Photomed*. 2019;35:3-10.

OCULAR COMPLICATIONS IN PHACE SYNDROME: A TRUE ASSOCIATION OR A COINCIDENCE?

PHACE syndrome is a constellation of findings in association with a typically segmental facial hemangioma. The E in this acronym stands for eye, referring to associated ocular complications. Samuelov et al looked retrospectively at all PHACE patients at their institution over a 15-year period to assess ocular risk. In their cohort of 30 patients, they found only 1 definite and 1 possible PHACE-related ocular complication. Another 7 patients had ocular concerns related to the physical presence of a periocular tumor rather than an underlying vasculopathy. No patients with hemangiomas distant to the eye had ocular complications. These data suggest that ophthalmologic evaluation is appropriate for patients with large periocular hemangiomas; however, ocular evaluation for infants without a periocular hemangioma, even when PHACE syndrome is considered, will likely be of low yield.

Samuelov L, Kinori M, Mancini AJ, et al. Ocular complications in PHACE syndrome: a true association or a coincidence? *J Pediatr*. 2019;204:214-8.

TREATMENT OF PEDIATRIC ALOPECIA AREATA WITH ANTHRALIN: A RETROSPECTIVE STUDY OF 37 PATIENTS

Short-contact therapy with anthralin is a well-recognized second-line treatment for pediatric alopecia areata. Wu et al examined 37 patients <17 years of age with anthralin-treated alopecia areata over an 11-year period at their institution. Most patients (65%) had patchy hair loss. Twelve patients (32%) achieved complete regrowth, and 25 patients (68%) experienced at least 50% regrowth. Improved response correlated with <50% scalp involvement and lack of prior treatment. The mean time to maximal response was 15 months. Four patients withdrew because of excessive irritation. Relapses occurred in 64% of patients with at least 50% maximal scalp regrowth. The authors concluded that anthralin is a safe and potentially effective intervention, limited by required duration of use, cutaneous irritation, and risk of relapse.

Wu S, Wang S, Ratnaparkhi R, Bergfeld W. Treatment of pediatric alopecia areata with anthralin: a retrospective study of 37 patients. *Pediatr Dermatol*. 2018;35:817-820.

MODULATION OF INFLAMMATORY GENE TRANSCRIPTS IN PSORIASIS VULGARIS: DIFFERENCES BETWEEN USTEKINUMAB AND ETANERCEPT

Brodmerkel et al examined the psoriasis disease transcriptome in 89 patients with moderate-to-severe psoriasis taking either ustekinumab or etanercept in the context of a phase 3 randomized, blinded trial. These investigators took pre- and post biopsies from the same psoriatic plaque to assess comparative drug effects on mRNA expressed in active lesions over time. Both drugs induced significant improvement in the study-specific transcriptome; however, ustekinumab demonstrated stronger and more durable suppression of not only interleukin 22 and 17, as might be expected mechanistically, but also of tumor necrosis factor α -related genes. The implications of this differential effect on gene expression despite similar clinical improvement (eg, Psoriasis Area and Severity Index $\geq 75\%$) are unknown but could have bearing on expected posttreatment course and for these and even next-generation agents.

Brodmerkel C, Li K, Garcet S, et al. Modulation of inflammatory gene transcripts in psoriasis vulgaris: differences between ustekinumab and etanercept. *J Allergy Clin Immunol*. 2019;143(5):1965-1969.

RANDOMIZED TRIAL OF FOUR TREATMENT APPROACHES FOR ACTINIC KERATOSIS

The authors compared the efficacy of 4 frequently used field-directed treatments for

multiple actinic keratoses (AKs) on the head in 624 patients treated during November 2014–March 2017. The median age of the trial participants was 75 years, and the population treated had a male-to-female ratio of 9:1. Patients were randomly assigned treatment with 5% fluorouracil cream, 5% imiquimod cream, methyl aminolevulinate photodynamic therapy, or 0.015% ingenol mebutate gel. The primary outcome was the proportion of patients with a reduction of $\geq 75\%$ in the number of AK lesions from baseline to 12 months after the end of treatment. At 12 months after the end of the respective treatments, fluorouracil treatment was found to be superior. With respect to fluorouracil, the hazard ratio (HR) for treatment failure with ingenol mebutate was 3.33, the HR with methyl aminolevulinate photodynamic therapy was 2.73, and the HR with imiquimod was 2.03. Satisfaction with treatment and improvement in health-related quality of life was highest in the fluorouracil group. The authors conclude that among the options studied, fluorouracil is the most effective for the treatment of multiple AKs.

Jansen MHE, Kessels JPHM, Nelemans PJ, et al. Randomized trial of four treatment approaches for actinic keratosis. *N Engl J Med*. 380;10:935-946.

DISTINCT CLINICOPATHOLOGICAL AND PROGNOSTIC FEATURES OF THIN NODULAR PRIMARY MELANOMAS: AN INTERNATIONAL STUDY FROM 17 CENTERS

Of the 4 subtypes of melanoma, the nodular subtype has the worst prognosis, and this worst prognosis is thought to be related to factors, such as thickness, ulceration, and mitotic rate. This study examined thin nodular melanomas <1 mm in thickness, from 17 cancer centers in the United States and Europe. Of 20,132 cases examined, T1 melanomas (9681) were primarily of superficial spreading type (96.8%), and only 3.8% were nodular subtype. These thin nodular melanomas occurred on the head and neck, were more likely to have mitoses histologically, and less likely to show regression. Five-year melanoma-specific survival was 75.4% for thin nodular melanomas and 91.0% for the superficial spreading counterpart. This was statistically significant and an independent variable by multivariate analysis, ie, not necessarily related to the other factors often associated with the prognosis of the nodular variant.

Dessinioti C, Dimou N, Geller A, et al. Distinct clinicopathological and prognostic features of thin nodular primary melanomas: an

international study from 17 centers. *J Natl Cancer Inst*. 2019. pii: djz034. [Epub ahead of print] doi/10.1093/jnci/djz034/5377294.

EXPRESSION OF P15 IN A SPECTRUM OF SPITZOID MELANOCYTIC NEOPLASMS

The accurate classification of spitzoid melanocytic lesions is challenging because of the overlapping clinical and histologic features among Spitz nevi, atypical Spitz tumors (ASTs), and spitzoid melanomas. Expression of p16 (*CDKN2A*) has been used as a marker of spitzoid lesions; however, its expression can be variable. p15 is a tumor suppressor encoded by *CDKN2B*, the loss of which has recently been shown to promote transition from nevus to melanoma. The authors sought to determine whether p15 is a useful immunohistochemical marker for distinguishing Spitz nevi from spitzoid melanomas and compared p15 and p16 staining for this purpose. Immunohistochemical staining for p15 and p16 was performed on Spitz nevi, ASTs, and spitzoid melanomas. Immunoreactivity was categorized by a 4-tiered system ranging from 0 (negative) to 3+ (strong). 3+ staining was observed in 68.4% of Spitz nevi, 34.2% of ASTs, and 17.7% of spitzoid melanomas. In contrast, the authors observed 3+ p16 staining in roughly equivalent percentages of Spitz nevi (57.9%), ASTs (56.1%), and spitzoid melanomas (58.8%). The authors conclude that p15 might be more useful than p16 as a biomarker to help distinguish benign from malignant spitzoid lesions.

Ma S, O'Day C, Dentchev T, et al. Expression of p15 in a spectrum of spitzoid melanocytic neoplasms. *J Cutan Pathol*. 2019;46(5):310-316.

DURABLE TUMOR REGRESSION AND OVERALL SURVIVAL IN PATIENTS WITH ADVANCED MERKEL CELL CARCINOMA RECEIVING PEMBROLIZUMAB AS FIRST-LINE THERAPY

Pembrolizumab is a programmed cell death 1 checkpoint inhibitor used as immunotherapy in advanced cancers; 50 patients with Merkel cell carcinoma who were naive to systemic therapy received pembrolizumab 2 mg/kg intravenously every 3 weeks for at least 24 weeks and up to 2 years. The group had a median 2.8-month response time. Overall, 69% of patients had a reduction in lesions; the overall response rate was 56%. Progression-free survival was 16.8 months, and the overall estimated 2-year survival was 68.7%. These outcomes compared favorably with the historical control of chemotherapy use alone. The authors cite this study of programmed cell death 1

therapy as demonstrating durable tumor control, a manageable safety profile, and favorable overall survival compared with historical data from patients treated with first-line chemotherapy.

Nghiem P, Bhatia S, Lipson EJ, et al. Durable tumor regression and overall survival in patients with advanced Merkel cell carcinoma receiving pembrolizumab as first-line therapy. *J Clin Oncol*. 2019;37(9):693-702.