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

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SEVERE AND PREDOMINANTLY ACTIVE ATOPIC ECZEMA IN ADULTHOOD AND LONG-TERM RISK OF CARDIOVASCULAR DISEASE: POPULATION-BASED COHORT STUDY

The authors studied data from UK electronic health records of primary care practices, matching 387,439 patients with atopic dermatitis to 1,528,477 patients without atopic dermatitis to determine whether adults with atopic dermatitis are at increased risk of cardiovascular disease and whether the risk varies by severity of atopic dermatitis and activity of the condition over time. The study showed that atopic dermatitis is associated with a moderately increased risk of nonfatal cardiovascular outcomes, with a dose-response for atopic dermatitis severity and cumulated activity. Patients with severe atopic dermatitis were at 20% increased risk of stroke; at 40% to 50% increased risk of unstable angina, myocardial infarction, atrial fibrillation and cardiovascular death; and at 70% increased risk of heart failure. Patients with the most active atopic dermatitis, defined as being active during more than 50% of the 5.1-year follow-up period, were at greater risk of cardiovascular disease.

Silverwood RJ, Forbes HJ, Abuabara K, et al. Severe and predominantly active atopic eczema in adulthood and long term risk of cardiovascular disease: population based cohort study. *BMJ*. 2018;361:k1786.

THE MICROBIOME IN ATOPIC DERMATITIS

Paller et al review the immunology and microbiology of the cutaneous microbiome in atopic dermatitis (AD). *Staphylococcus aureus* is known to colonize most patients with AD; Paller et al review the complex interplay between *S aureus* and commensal skin species, as well as the implications for both treatment and prevention of AD. *S aureus* does more than infect the skin: it damages the skin barrier, modulates the inflammatory response, and contributes to decreased bacterial diversity during AD flares. Certain coagulase-negative *Staphylococcus* species and other skin commensals such as *Roseomonas* help control *S aureus* colonization, and emerging evidence suggests that application to the skin of affected patients can improve itch, rash, and quality of life. Many questions remain, including questions regarding the wisdom of current microbiocidal practices routinely used to treat AD, as well as the potential for an anti—*S aureus* vaccine.

Paller AS, Kong HH, Seed P, et al. The microbiome in atopic dermatitis. *J Allergy Clin Immunol*. 2018;143:26-35.

DUPILUMAB PROGRESSIVELY IMPROVES SYSTEMIC AND CUTANEOUS ABNORMALITIES IN PATIENTS WITH ATOPIC DERMATITIS

Dupilumab is an anti—interleukin 4/13 (IL-4/13) antibody that is now approved for the treatment of moderate-to-severe atopic dermatitis (AD) in adults. Guttman-Yassky et al performed a double-blind placebo controlled-trial of 54 adults looking at safety, efficacy, and specific molecular effects in lesional and nonlesional skin. This study demonstrates dupilumab's ability to modulate AD inflammation and positively affect the skin barrier, and it further correlates tissue-level therapeutic response and amplitude of anti-inflammatory effect. Dupilumab reversed key immunologic and barrier abnormalities in patients with AD beyond what might be expected from IL-4/13 blockade alone, including effects on keratinocytic proteases, T-cell activation, and both the IL17 and IL22 pathways. This study confirms the

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central role of type 2 helper T-cell–driven inflammation in AD pathogenesis while also demonstrating how dupilumab can mitigate the inflammatory signature in both skin and blood.

Guttman-Yassky E, Bissonnette R, Ungar B, et al. Dupilumab progressively improves systemic and cutaneous abnormalities in patients with atopic dermatitis. *J Allergy Clin Immunol*. 2019;143:155-172.

EFFICACY AND ABSORPTION OF TOPICAL SIROLIMUS FOR THE TREATMENT OF VASCULAR ANOMALIES IN CHILDREN: A CASE SERIES

The authors studied the use of topical sirolimus in 6 children aged 2 to 17 years who had lymphatic and vascular anomalies. In all, 3 superficial lymphatic malformations demonstrated a rapid decrease in size and a significant decrease in discharge and oozing. The responses occurred in less than 3 months. Another 3 lesions did not respond; specifically, a fourth lymphatic malformation (that was truncular as opposed to the responding lesions, which were extratruncular), a verrucous venous malformation, and an infantile hemangioma did not respond. Adverse effects were limited to local irritation. Measured blood levels of sirolimus were insignificant; the authors noted no systemic side effects, and because of the low blood levels, they predicted that there would be none. The authors speculate that lack of efficacy of topical sirolimus in the infantile hemangioma and the verrucous venous malformation was related to the lack of a lymphatic component in these lesions. They offer topical sirolimus as an efficient and well-tolerated treatment for children with cutaneous manifestations of extratruncular lymphatic malformations.

Le Sage S, David M, Dubois J, et al. Efficacy and absorption of topical sirolimus for the treatment of vascular anomalies in children: a case series. *Pediatr Dermatol*. 2018;35:472-477.

Garcia-Montero P, Del BJ, Sanchez-Martinez M, Escudero Santos IM, Baselga E. Microcystic lymphatic malformation successfully treated with topical rapamycin. *Pediatrics*. 2017;139(5):pii: e20162105.

SKIN CANCER PHOTOTYPE: A NEW CLASSIFICATION DIRECTLY RELATED TO SKIN CANCER AND BASED ON RESPONSES FROM 2869 INDIVIDUALS

The authors observe that the Fitzpatrick skin type, which is the near-universal metric for describing the skin's response to ultraviolet light, was designed to describe the ability to tan and the ability to burn and to thus be used for selecting a suitable dose of ultraviolet A in psoralen plus ultraviolet A therapy. It has become a proxy for the measurement of skin cancer risk, but it was not designed to serve this purpose. The authors undertake to create a skin cancer phototype (SCP) classification with direct relation to skin cancer risk based on the questions used in Fitzpatrick's phototype classification. They separate the questions regarding tanning and burning into 2 separate components, citing the reciprocal interdependence between tendency to burn and ability to tan. They also measure participants' skin phototype with the pigment protection factor, which equals the number of standard erythema doses needed to elicit perceptible erythema. The authors arrive at 4 SCPs. SCP I has an odds ratio for the development of all skin cancers of 5.35, SCP II has an odds ratio of 4.58, and SCP III has an odds ratio of 2.59, with SCP IV having the benchmark odds ratio of 1. The authors offer the SCP as a classification directly related to skin cancer risk.

Holm-Schou AS, Philipsen PA, Wulf HC. Skin cancer phototype: a new classification directly related to skin cancer and based on responses from 2869 individuals [e-pub ahead of print]. *Photodermatol Photoimmunol Photomed*. https://doi.org/10.1111/phpp.12432. Accessed December 20, 2018.

PATIENT KNOWLEDGE OF FDA-MANDATED SUNSCREEN LABELING TERMINOLOGY: A CROSS-SECTIONAL SURVEY

The authors reference the US Food and Drug Administration 2011 final rule on sunscreen labeling, which was introduced to simplify and standardize sunscreen terminology, and to "ensure the proper use of these sunscreens and greater consumer protection from the damaging effects of ultraviolet radiation." They authors observe that there is little knowledge of actual patient comprehension of the resulting terminology, and they undertake to study the degree to which supposedly consumer-friendly terminology is actually understood by the public. The results of the study showed general understanding of the language of sunscreen labeling to be poor. A total of 3 questions were posed: what does sun protection factor on sunscreen labels represent? in reference to sunscreen, what does broad-spectrum mean? and can sunscreen be waterproof? Multiple-choice answers were offered. Before testing, when subjects were asked to characterize their own understanding of sunscreen labeling terminology, 33.7% of respondents characterized their understanding as excellent or very good. When given the test, 8.7% of subjects answered all 3 questions correctly. The authors point to the gap between the US Food and Drug Administration's intentions and consumer understanding and call for greater public education efforts.

Prado G, Svoboda R, Teplitz RW, Farberg AS, Rigel DS. Patient knowledge of FDA-mandated sunscreen labeling terminology: a cross-sectional survey [e-pub ahead of print]. *Photodermatol*

Photoimmunol Photomed. https://doi.org/10.1111/phpp.12437. Accessed December 20, 2018.

COMPENSATION BEHAVIORS AND SKIN CANCER PREVENTION

The authors divided sun minimization strategies into 3 types: protection (sun screen), avoidance (seeking shade), and cover-up (wearing protective clothing or a hat). They observed that numerous studies have investigated the use of sun minimization strategies but few have addressed combinations of different strategies. They set out to test the compensation hypothesis, which suggests that the use of 1 strategy results in a decrease in use of others. They found that for all strategies, older respondents performed minimization more regularly. Different strategies were rarely used in combination. Protection alone was reported as being used most often (21.8%), and only 5.7% of respondents used all 3 strategies simultaneously. Correlations showed that avoidance was positively correlated with covering up at 0.46, but only weakly with protection at 0.09, and that protection and covering-up were not correlated at all. In all, 38% of the subjects in the sample did not practice any ultraviolet protection strategy at all. The authors found that the subjects who did practice a strategy tended use 1 type of strategy to compensate for not using another, resulting in less sun protection. They call for specific health messaging to encourage use of multiple protection strategies.

Bleakley A, Lazovich D, B Jordan A, Glanz K. Compensation behaviors and skin cancer prevention. *Am J Prev Med*. 2018;55(6):848-855.

RISK FACTORS FOR DEVELOPMENT OF NEW SKIN NEOPLASMS IN PATIENTS WITH PAST HISTORY OF SKIN CANCER: A SURVIVAL ANALYSIS

The authors observe that although it is well known that patients with a first-time diagnosis of skin cancer carry an increased risk of developing subsequent skin neoplasms, the degree of increased risk has been insufficiently quantified and associated epidemiologic factors have not been adequately identified. This study assesses the risk and associated risk factors of development of subsequent skin cancers after receiving a first diagnosis of skin cancer. The authors analyzed 969 patients with a total of 1584 skin neoplasms: 1122 basal cell carcinomas (BCCs), 310 squamous cell carcinomas (SCCs), 143 melanomas, and 9 other neoplasms. They found that a diagnosis of an initial BCC conferred an adjusted hazard rate (HR) of 1.63 for subsequent BCCs and an initial diagnosis of SCC conferred an HR of 3.6 for subsequent SCCs. Associated epidemiologic risk factors included older age (HR, 1.04/y), with patients who developed new neoplasms having an average age of 69 years versus 63 years for those who did not. The presence of synchronous neoplasms at first diagnosis conferred an HR of 2.25, with 33.3% of patients with synchronous neoplasms at first diagnosis developing subsequent neoplasms versus 15.3% of those with initial diagnosis of a single lesion. The authors stress the need for careful follow-up of patients in whom an initial skin cancer has been diagnosed.

Duarte AF, Sousa-Pinto B, Haneke E, Correia O. Risk factors for development of new skin neoplasms in patients with past history of skin cancer: a survival analysis. *Sci Rep*. 2018;8:15744.

HOST CHARACTERISTICS AND RISK OF INCIDENT MELANOMA BY BRESLOW THICKNESS

This study examined the association between clinical attributes and the risk of development of a thin melanoma or a thick melanoma. Two cohorts were studied over 22 to 30 years: the Nurses' Health Study (I and II) and the Health Professionals Follow-up Study cohorts. The patients had to answer a questionnaire. These self-referral cohorts consisted of close to 300,000 patients and had a response rate higher than 90%. The patients were queried about their hair color, number of nevi, sites of nevi, family history of melanoma, and history of blistering sunburns during different stages of their lives. The study found that both women and men with a family history of melanoma were more likely to develop thick melanomas, with men with more nevi being more likely to develop thick melanomas. None of the other surveyed parameters such as hair color or tendency to burn were found to be of predictive value.

Li WQ, Cho E, Wu S, Li S, Matthews NH, Qureshi AA. Host characteristics and risk of incident melanoma by Breslow thickness. *Cancer Epidemiol Biomarkers Prev*. 2019;28(1):217-224.

EFFICACY OF NOVEL IMMUNOTHERAPY REGIMENS IN PATIENTS WITH METASTATIC MELANOMA WITH GERMLINE *CDKN2A* MUTATIONS

Carriers of cyclin dependent kinase inhibitor 2A gene (*CDKN2A*) mutation who developed metastatic melanoma and who underwent immunotherapy treatments were identified among carriers enrolled in follow-up studies for familial melanoma. The carriers' responses to immunotherapy treatments were compared with the responses reported in phase III clinical trials for cytotoxic T-lymphocyte associated protein 4 and programmed cell death 1 inhibitors. Melanomas with somatic *CDKN2A* mutation were analyzed for association with tumor mutational load. In melanomas with somatic

CDKN2A mutations, there were significantly higher total numbers of mutations in their genome than in the tumors without *CDKN2A* mutation. No significant differences were found in the mutation load depending on whether tumors had mutations in B-Raf proto-oncogene, serine/threonine kinase gene (*BRAF*) or NRAS proto-oncogene, GTPase gene (*NRAS*). The study found that 11 of 19 *CDKN2A* carriers responded to immunotherapy, with 6 of the 19 *CDKN2A* carriers (32%) having a complete response, which is a significantly higher frequency than that observed in the clinical trials. The authors speculate that patients with *CDKN2A*-mutated melanoma may have improved immunotherapy responses on account of increased mutational load, resulting in more neoantigens and stronger antitumorous immune responses.

Helgadottir H, Ghiorzo P, van Doorn R, et al. Efficacy of novel immunotherapy regimens in patients with metastatic melanoma with germline *CDKN2A* mutations [e-pub ahead of print]. *J Med Genet*. https://doi.org/10.1136/jmedgenet-2018-105610. Accessed December 20, 2018.

JAAD Game Changers: Clinical outcomes and response of patients applying topical therapy for pyoderma gangrenosum: A prospective cohort study

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Capsule Summary	• Pyoderma gangrenosum is a painful ulcerating disease. The current evidence base for treatment is limited. • In a large prospective study of topical treatments, 44% of patients were healed by 6 months. Ulcer size was a predictor of healing, and 15% of patients with pyoderma gangrenosum had a recurrence. • Clobetasol propionate 0.05% is a potentially useful first-line therapy for patients with pyoderma gangrenosum, particularly for patients with small lesions.
How did this article change the practice of dermatology?	Although this treatment is often given in clinical practice, this study confirms that high-potency topical steroids for solitary and small pyoderma gangrenosum lesions is an appropriate first-line therapy with 44% of patients healing by 6 months. Larger ulcerations might need more intensive therapy.[1]

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