Dermatitis Research Review™

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Abbreviations used in this issue:

AD = atopic dermatitis; **CI** = confidence interval; **EASI** = Eczema Area and Severity Index; **Ig** = immunoglobulin; **IGA** = Investigator Global Assessment; **IL** = interleukin; **ISGA** = Investigator's Static Global Assessment; ***MBP*** = myelin basic protein gene.

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Welcome to the first issue of Dermatitis Research Review for 2022.

A study utilising machine-learning–based technology to perform deep phenotyping of atopic dermatitis (AD) published in *JAMA Dermatology* identifies factors associated with risk of severe disease in adolescent and adult patients such as disease onset after 12 years of age and atopic stigmata, a Taiwanese study finds a correlation between hypomethylation within the *Golli-Myelin Basic Protein (MBP)* locus of the *MBP* gene and severity of childhood AD indicating it may act as a biomarker. Emollient application from birth on an as needed basis may be a simple and low-cost intervention to reduce the burden of allergic disease in tropical climates with a Thai study demonstrating that this approach is feasible for AD prevention. Crisaborole ointment demonstrated efficacy for mild-to-moderate AD in a Japanese paediatric intra-patient trial and may constitute a novel treatment option for this population and results from Pfizer's international JADE REGIMEN trial show that oral abrocitinib is an efficacious induction regimen for moderate-to-severe disease and is capable of effectively re-establishing disease control after drug withdrawal, suggesting that it is suitable for a real-world population where non-compliance may be an issue. Finally, we discuss the incidence of dupilumab-associated psoriasiform dermatitis in paediatric patients and look at the evidence from a repeated open application test study conducted by the Danish National Allergy Research Centre regarding the development of dermatitis in children with aluminium contact allergy after exposure to sunscreen containing aluminium.

We hope you find these and the other selected studies interesting, and wish you a safe and happy New Year.

Kind Regards,

Dr John Frew
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Machine learning–based deep phenotyping of atopic dermatitis severity-associated factors in adolescent and adult patients

Authors: Maintz L et al.

Summary: Maintz et al utilised a machine learning–gradient boosting approach in conjunction with multinomial logistic regression to analyse cross-sectional data and identify factors associated with an increased odds of severe AD. A total of 367 patients at least 12 years of age, predominantly adults (94%; mean age 39 years), treated at the University Hospital Bonn in Germany were included in the study. Almost half of the study cohort (48.2%) had mild disease with an Eczema Area and Severity Index (EASI) score of ≤ 7, approximately one-third (32.7%) had moderate disease (EASI >7 to ≤ 21) and 19.1% had severe disease (EASI >21). Nine factors were found to be associated with a higher probability of severe AD: age (bimodal distribution with peaks at 12-21 years and > 52 years), disease onset after 12 years of age, total serum immunoglobulin (Ig) E level > 1708 IU/mL, eosinophil values > 6.8%, physical cutaneous markers (atopic stigmata such as cheilitis, white dermographism, Hertoghe sign or nipple eczema), male sex, physical activity less than once per week, smoking and alopecia areata. Machine learning–gradient boosting and multinomial logistic regression had comparable predictive performance (mean multiclass area under the curve value: 0.71 vs 0.68, respectively).

Comment: Machine learning and artificial intelligence have great potential in medicine to identify patterns and relationships not immediately apparent to practicing clinicians. This is particularly true in the field of biomarkers, where clinical and molecular markers can identify subgroups of patients more amenable to specific disease associations, complications or response to therapies. This prospective cross-sectional study used machine learning to identify clinical markers more associated with disease severity in AD. Specific clinical associations including Hertoghe's sign and nipple eczema were significantly associated with more severe AD, as well as IgE levels above 1708 IU/ mL. The important thing to acknowledge in manuscripts such as this one is, although there is a statistical significance in the relationship between these markers and severity, is the relationship also clinically significant? This is still an outstanding question and hence the results in this paper should be taken with a grain of salt until evidence emerges that such markers can clinically impact patient management in a real-world setting.

Reference: JAMA Dermatol 2021;157(12):1414-24
Abstract

DNA methylation array identifies Golli-*MBP* as a biomarker for disease severity in childhood atopic dermatitis

Authors: Chen K-D et al.

Summary: Comparison of peripheral blood epigenome-scale methylation events with DNA methylation arrays between patients with childhood AD and controls enabled analysis of epigenetic changes in AD in this Taiwanese study. Analysis of 48 participants, 24 with AD and 24 controls, identified 16,840 GC-rich regions differentially methylated in patients with AD, most of which (97%) were unmethylated (hypomethylated compared to controls). Using subnetwork enrichment analysis, pyrosequencing in an independent cohort (n=224) and multivariate correlation analysis the researchers found that reduced methylation of one of the two identified GC-rich regions (cg24700313) within the *Golli-MBP* locus of the *MBP* gene was associated with AD severity and increased IgE levels. The authors concluded that hypomethylation of this region in the *Golli-MBP* locus maybe correlated to childhood AD severity and constitute a biomarker for such.

Comment: Markers of disease severity risk in AD would allow clinicians to aggressively manage those patients who are at high risk of developing severe disease through patient stratification. As seen in the previous manuscript- many statistical associations of clinical or blood biomarkers have not yet been validated as being clinically relevant. This DNA methylation study also identifies a specific methylation marker in the *Golli-MBP* locus. The independent validation of this methylation marker in a separate cohort of AD patients and healthy controls highlights this marker as being both statistically and clinically relevant. It was interesting that the marker did not significantly correlate with serum IgE levels, the reasons for which remain incompletely understood. Given that many emerging therapies can impact DNA methylation status, this biomarker-based study helps us to understand the pathogenesis of AD more thoroughly, as well as potentially identify new ways of stratifying disease severity in AD.

Reference: J Invest Dermatol 2022;142(1):104-13
Abstract

Abrocitinib induction, randomised withdrawal, and retreatment in patients with moderate-to-severe atopic dermatitis

Authors: Blauvelt A et al.

Summary: Results from the JAK1 Atopic Dermatitis Efficacy and Safety (JADE) REGIMEN phase 3 trial, published in *Journal of the American Academy of Dermatology*, demonstrate the efficacy of abrocitinib as an induction therapy and for rescue following disease flare in patients with moderate-to-severe AD. The international Pfizer-sponsored trial (ClinicalTrials.gov Identifier: NCT03627767) enrolled 1,233 paediatric (at least 12 years of age) and adult patients with moderate-to-severe AD (≥ 10% body surface area impacted, ≥ 3 Investigator's Global Assessment [IGA] score, ≥ 16 EASI score and pruritus numerical rating scale ≥ 4) from sites across North America, Europe, China and Taiwan. Responders to a 12-week open-label 200 mg abrocitinib monotherapy induction regimen (defined as achieving an IGA 0/1 plus reduction of ≥ two-points and an EASI-75 response; n=798; 64.7%) were randomised to one of the three 40-week blinded trial arms and received oral abrocitinib maintenance at a dose of 100 or 200 mg/day or placebo. Significantly higher rates of disease flare requiring rescue treatment with abrocitinib 200 mg plus topical therapy were found in the placebo arm (80.9% vs 18.9% vs 42.6% with abrocitinib 100 mg or 200 mg maintenance). High rescue rates were reported in the cohort who did not receive abrocitinib maintenance (81.6% re-achieved IGA 0/1 response and 91.8% re-achieved EASI response).

Comment: One of the difficulties in applying clinical trial data to the real-world setting is knowing what happens when the drug is withdrawn and then re-introduced. Patients may temporarily withhold a medication for many reasons including illness (including over the last few years of the coronavirus disease 2019 [COVID-19] pandemic), vaccination, pregnancy and non-compliance. Many biologic medications carry the risk of developing antidrug antibodies after periods of withdrawal and reintroduction, but theoretically, small molecular inhibitors such as JAK inhibitors should be spared such events. This analysis of clinical trial data including randomisation of participants with clinical response to abrocitinib, demonstrates a high level of efficacy "recapture". In individuals responding to 200 mg of abrocitinib and then consequently given placebo, 80.9% of participants flared and 91.8% of those regained control with the reintroduction of abrocitinib. This gives important causal evidence to the fact that withdrawal and reintroduction of abrocitinib is able to re-establish effective disease control in a majority of individuals.

Reference: J Am Acad Dermatol 2022;86(1):104-12
Abstract

Scratching the surface: a review of online misinformation and conspiracy theories in atopic dermatitis

Authors: O'Connor C & Murphy M

Summary: In this concise report by two researchers affiliated with the South Infirmary Victoria University Hospital and University College Cork, both in Ireland, the consequences and magnitude of the misinformation regarding treatments and aetiology of AD online was described. A search of PubMed yielded one relevant scientific review that found a low quality of eczema-related videos on YouTube and this was substantiated by a Google search that revealed a plethora of misinformation readily available ranging from false or unproven cures such as avoidance of certain foods, chemicals, vaccines, dust, apple cider vinegar or witch hazel to incorrect aetiologies including formaldehyde, detergents and even 5G wireless technology. Deleterious consequences of this misinformation can be extreme with fatalities reported due to nutritional deficiencies among other examples. Awareness of this AD-related misinformation may aid dermatologists to combat it.

Comment: As physicians we are commonly asked to address issues patients have identified online. In this age of misinformation, a number of common misconceptions are touted online as both the cause of AD and quick cures which can eliminate the disease. This interesting article updates dermatologists regarding common misconceptions and conspiracies, including reports that vaccines cause AD, that severe dietary restriction can cure dermatitis, as well as common posts and threads regarding "topical steroid addiction". Specific published articles from renowned dermatologic societies are referenced with evidence-based rebuttals to some of these misconceptions which can be practically used for patient education purposes.

Reference: Clin Exp Dermatol 2021;46(8):1545-47
Abstract

Independent commentary by Dr John Frew, *MBBS (Hons) MMed (Clin Epi) MSc FACD*

Dr John Frew is a fellow of the Australasian College of Dermatologists and researcher in the field of inflammatory skin diseases with a focus on hidradenitis suppurativa. He holds a staff specialist position at Liverpool Hospital, and is a conjoint lecturer at the University of New South Wales supervising dermatology trainees and postgraduate research students. He completed his post-doctoral fellowship at the Rockefeller University in New York City identifying immunological pathways and novel therapies for the treatment of hidradenitis suppurativa. Dr Frew has over 100 peer-reviewed publications and contributions to international dermatology and immunology textbooks in the field of inflammatory skin disease.

Effects of an emollient application on newborn skin from birth for prevention of atopic dermatitis

Authors: Techasatian L & Kiatchoosakun P

Summary: This randomised controlled study in Thai neonates reports a favourable protective effect of emollient use on an as needed basis on AD development. Healthy full term (gestational age > 37 weeks) high-risk infants less than three weeks of age with a first degree relative diagnosed with an allergic disease such as AD, asthma or allergic rhinitis were enrolled from the paediatric department of Khon Kaen University in Thailand and randomised to undergo a six-month treatment with skin care advice ± moisturiser. The cumulative incidence of AD diagnosis was significantly lower in the emollient trial arm, with the reduction in the risk of AD greater than half (relative risk 0.39; 95% confidence interval [CI], 0.24-0.64; $p<0.001$). Significant benefits in delayed development of disease and lower severity were also reported after emollient use. The observation that low versus moderate adherence to emollient application resulted in a lower incidence of AD at six-months ($p=0.008$) led the study authors to conclude that application on an as needed basis as opposed to a daily regimen imparted greater benefit in a tropical climate setting. Adverse events reported at higher frequencies in the emollient group included miliaria and impetigo. In utero and neonatal exposure to passive smoking was also associated with greater risk of AD development ($p<0.001$).

Comment: Studies establishing the effective role of preventative emollients in the setting of AD risk have largely been performed in Europe and North America. Environmental factors including heat and humidity are known to play a role in the activity of AD, however such emollient-based studies (and their potential adverse events) have not been replicated in a tropical setting. This Thai study identifies that daily emollient application was associated with a higher risk of miliaria and impetigo than 'as needed' emollient application over a six-month period. Certainly, a stronger risk factor for disease activity in this population was exposure to passive smoking both pre- and postnatally, however it is important to tailor treatment messages to the population and climate. This study was limited by the short follow-up period but raises interest in the inherent bias with many studies not replicated in tropical and sub-tropical nations and climates.

Reference: J Eur Acad Dermatol Venereol 2022;36(1):76-83
Abstract

A phase 2b, randomized, double-blind, multicentre, vehicle-controlled study to assess the efficacy and safety of two crisaborole regimens in Japanese patients aged 2 years and older with mild-to-moderate atopic dermatitis

Authors: Fujita K et al.

Summary: This Japanese phase 2b, intra-patient trial (NCT03954158) assessed the efficacy of topical 2% crisaborole ointment for mild-to-moderate AD. A total of 81 patients were accrued from three sites into two cohorts - ≥ 12 years (n=41) and 2-11 years (n=40) and randomised to a two-week treatment with once- or twice-daily crisaborole 2% regimens. Two target lesions of moderate severity (Investigator's Static Global Assessment [ISGA] 3) at least 10 cm apart and ≥ 3 cm x 3 cm were each randomised to crisaborole or vehicle. The primary efficacy outcome measure of improvement in total sign score (TSS) that considered the severity of erythema, induration/papulation, excoriation and lichenification showed that both regimens of crisaborole elicited significantly greater reductions in TTS at day 15 compared to vehicle in both the younger paediatric and older cohorts with a greater absolute magnitude of benefit with the twice daily application (≥ 12 year old cohort; approximate mean change in TSS at day 15, -4.5 vs -4.8 vs -2.6; 2-11 year old cohort, -3.4 vs -4.6 vs -2.2; all $p<0.01$). Compared to vehicle, benefits were also seen in ISGA, peak pruritus numerical rating scale, Itch Severity scale and Caregiver-Reported Itch Severity numerical rating scale in both crisaborole regimens in all cohorts. Site irritation was the most commonly reported treatment-emergent adverse event.

Comment: The number of highly efficacious treatments for moderate-to-severe AD has altered the treatment landscape dramatically. However, in the setting of mild-to-moderate disease, more options are needed in order to alleviate concern regarding topical corticosteroid use. This phase 2 study in Japanese children identifies crisaborole both daily and twice-daily application as demonstrating significant benefit in individual lesions of AD when compared to vehicle only. Irritation at the site of application was the most commonly reported adverse event similar to the international phase 2 study reported in 2020. Overall, crisaborole demonstrated positive impact and good safety profile both in this study and in multiple other global studies indicating it can be a useful option for children with mild-to-moderate AD.

Reference: J Dermatol 2021;48(11):1640-51
Abstract

Psoriasiform dermatitis during dupilumab treatment for moderate-to-severe atopic dermatitis in children

Authors: Parker JJ et al.

Summary: Retrospective review of paediatric patients undergoing dupilumab therapy for severe AD by a group affiliated with six US hospitals including Northwestern University Feinberg School of Medicine, Icahn School of Medicine at Mount Sinai and Stanford University School of Medicine has identified six cases of dupilumab-induced psoriasiform dermatitis. The cohort were aged between four and 18 years of age (median age 13 years), achieved a clinically meaningful response to dupilumab therapy as evidenced by a 13-point reduction in IGA but developed psoriasiform lesions at between six and 12-months after treatment initiation (median eight months). New onset psoriasiform plaques were most commonly located on the extremities, scalp, face, ears and trunk, generally away from AD lesions and were easily distinguishable from AD with a bright red colour, sharp demarcated borders and thick lesional scale. Monomorphic pustules were also noted on a single patient. Exacerbation of pre-existing but previously undiagnosed concomitant psoriasis was revealed on a seventh child. Treated-associated psoriasiform lesions in paediatric patients seemed to be less refractory than those reported in adult patients with psoriasiform lesions completely cleared in four patients and partially cleared in another patient within two months of topical moderate-potent strength corticosteroid ointment administration and any recurrent lesion appearance also managed. All but one patient continued dupilumab therapy.

Comment: Case reports of psoriasiform eruptions in the setting of dupilumab therapy have been reported in both adults and children. It is unclear whether this represents a true drug reaction or an 'unmasking' of lesions of an eczema-psoriasis overlap syndrome- particularly in children. This case series identifies seven children, six of which had psoriasiform lesions which responded to topical corticosteroids and a seventh with true psoriasis alongside severe atopic dermatitis. Given the close relationship between TH2 and TH1/Th17 immune polarisation it is conceivable that suppression of the Th2 axis (via interleukin [IL]-4 and IL-13 blockade) can then lead to an upregulation in TH17 pathways leading to the development or unmasking of psoriasis like lesions. This is a rare but important adverse effect to acknowledge with only further cases and reporting able to establish the most effective and safe treatment modality for management.

Reference: Pediatr Dermatol 2021;38(6):1500-5
Abstract

Ideal proportion of the population to be patch tested: How many should we be doing?

Authors: Mughal A et al.

Summary: This study was conducted in collaboration with the British Society for Cutaneous Allergy in order to provide an updated analysis of the minimum population proportion that should be patch tested for allergic contact dermatitis. Eleven patch test centres across the UK and the Republic of Ireland contributed data from 2015 to 2017, inclusively, for retrospective analysis. Analysis of the optimal proportion of the population to be tested revealed that in the 20-year interval since this data was last reported the minimum proportion required to be tested had increased from 1:700 to 1:550 per head of population per annum.

Comment: The incidence of allergic contact dermatitis continues to evolve over time, as well as the most common causative allergens. Examining the rate of relevant positive responses can give an indication as to the utility of patch testing and whether the threshold for referring patients for patch testing should be increasing or decreasing. This study is a replica of a previous study approximately 20 years previously. It indicates that the rates of relevant positive reactions are increasing. In the UK the estimated proportion of individuals who would benefit from patch testing has increased from 1 in 700 to 1 in 550. This suggests that along with the previously reported shifts in common allergens over the past 20 years, that general rates of contact dermatitis are increasing, translating to dermatologists considering a slightly lower threshold to undertake patch testing.

Reference: Contact Dermatitis 2021;85(6):693-97
Abstract

Does aluminium in sunscreens cause dermatitis in children with aluminium contact allergy

Authors: Hoffmann S et al.

Summary: A repeated open application test study conducted by the Danish National Allergy Research Centre concludes that cutaneous contact dermatitis may develop in paediatric patients diagnosed with contact allergy to aluminium. The study accrued 16 patients between the ages of two and nine years old (mean age five years) from Gentofte Hospital who had a symptomatic vaccine granuloma after receipt of an aluminium-adsorbed vaccine and had a positive patch test to aluminium chloride hexahydrate petrolatum (2%, or 10% if eight years or older). Patients underwent a two-week trial consisting of twice-daily parallel application of an aluminium-containing sunscreen and a sunscreen without aluminium (Derma sun lotion SPF 30 Baby with an aluminium content of 1620 mg/kg and Änglamark sun lotion SPF 30 with an aluminium content ≤ 4 mg/kg, respectively, confirmed by inductively coupled plasma mass spectrometry) to two separate areas on the lower back. Application of 0.2 mL of cream equated to an aluminium exposure of 32.4 µg per application. No reactions to sunscreen without aluminium were observed. A single child obtained a positive reaction to the aluminium-containing sunscreen consisting of erythema and papules (rated a repeated open application test study score of 7/18). Exacerbation of granuloma pruritus was also reported in seven children.

Comment: The use of metals including zinc, titanium and aluminium in sunscreens can often lead to questions by concerned parents. Whilst allergy to aluminium is not common, the relevance of this metal in a sunscreen formulation is unclear. This small case series identified seven children with documented positive patch test reactions to aluminium to repeat open application patch test (with relevant sunscreen controls). Only one of the seven children had a positive reaction. This suggests that even in the setting of positive patch testing to aluminium that the relevance of this excipient in sunscreens may vary on a case-by-case basis. Open application testing may be useful in this regard to establish whether aluminium based sunscreens are safe to apply in this setting.

Reference: Contact Dermatitis 2022;86(1):9-14
Abstract

Occupational contact dermatitis in hospital cleaning workers

Authors: Tuncay Taş A et al.

Summary: This cross-sectional study from Turkey utilised a questionnaire approach in combination with physical examination, patch test, skin biopsy and total IgE investigation to examine the prevalence of occupational contact dermatitis in hospital cleaning workers. More than one-fifth of the study cohort (n=236) had occupational contact dermatitis, which was more than twice as prevalent in female versus male workers (26.4% vs 11%). Four independent risk factors were identified for occupational contact dermatitis – female sex, low educational level, cleaning the external surfaces of the medical equipment and mixing the cleaning products.

Comment: Given the significant increase in infectious disease concern over the past two years, as well as the increase in use of cleaning products in all facets of day-to-day life, it is unsurprising that rates of occupational irritant and contact dermatitis have increased. One occupational group with a significant burden of occupational dermatitis includes hospital cleaners. This cross-sectional study identified a greater than one in five incidence of occupational contact dermatitis. The significant disparity between male and female workers was noted. Given the critical functions these workers provide, acknowledgement of occupational complications and timely identification and management are important. Given that this is a Turkish study, locational and cultural factors may have influenced the results and it would be of interest to compare the results of this study to other sites globally.

Reference: Dermatitis 2021;32(6):388-96
Abstract

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