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Pilot study measuring transepidermal water loss (TEWL) in children suggests trilipid cream is more effective than a paraffin-based emollient

Sayantani Sindher^{1,2}, Shifaa S. Alkotob^{1,2}, Melanie N. Shojinaga^{1,2}, Helen A. Brough^{3,4,5}, Henry T. Bahnson⁶, Susan Chan^{3,4,5}, Gideon Lack^{3,4,5}, Donald Y. M. Leung^{7,8}, Kari C. Nadeau^{1,2}

¹Sean N. Parker Center for Allergy and Asthma Research at Stanford University School of Medicine, Stanford, CA, USA

²Division of Pulmonary and Critical Care Medicine, Department of Medicine, Stanford University, Stanford, CA, USA

³Paediatric Allergy Group, Department of Women and Children's Health, School of Life Course Sciences, King's College London, St. Thomas' Hospital, London, UK

⁴Paediatric Allergy Group, Peter Gorer Department of Immunobiology, School of Immunology & Microbial Sciences, King's College London, Guys' Hospital, London, UK

⁵Children's Allergy Service, Evelina Children's Hospital, Guy's and St. Thomas' Hospital NHS Foundation Trust, London, UK

⁶Immune Tolerance Network, Benaroya Research Institute, Seattle, WA, USA

⁷Department of Pediatrics, National Jewish Health, Denver, CO, USA

Correspondence: Kari C. Nadeau, Director, Sean N. Parker Center for Allergy and Asthma Research at Stanford University, 269 Campus Drive, CCSR 3215, MC 5366, Stanford, CA 94305-5101, USA. knadeau@stanford.edu.

CONFLICT OF INTEREST

Dr Sayantani Sindher reports grants from Aimmune, DBV Technologies, and Regeneron; Dr Helen A Brough reports grants from Food Allergy Research & Education (FARE), being on the UK advisory Board for DBV Technologies, and research support from Thermo Fisher Scientific; Dr Bahnson reports personal fees from King's College, London, UK, and DBV technologies; Dr Susan Chan reports nonfinancial support from Aimmune and grant support from Novartis; Dr Gideon Lack holds shares in DBV Technologies and from Mighty Mission Me, has consulted for Novartis, Sanofi-Genzyme, Regeneron, ALK-Abello, and has received funding from National Institute of Allergy and Infectious Diseases (NIAID, NIH), MRC & Asthma UK Centre, UK Dept of Health through NIHR, National Peanut Board, Action Medical Research, The Davis Foundation, and ICAP Charity; Dr Donald Leung is supported by NIH grants 5AR41256, 1U19AI117673, UL1TR002535 and UM1AI130780, is a recipient of the Edelstein Family Chair of Pediatric Allergy-Immunology at National Jewish Health, has received grant support from Pfizer, Incyte and MedImmune/A-Z, consulted for Sanofi-Genzyme, Regeneron, Aimmune Therapeutics and Janssen Pharmaceuticals; Dr Kari Nadeau reports grants from National Institute of Allergy and Infectious Diseases (NIAID), Food Allergy Research & Education (FARE), End Allergies Together (EAT), Allergenix, and Ukko Pharma, is a grant awardee at NIAID, National Institute of Environmental Health Sciences (NIEHS), National Heart, Lung, and Blood Institute (NHLBI), and the Environmental Protection Agency (EPA), is involved in clinical trials with Regeneron, Genentech, Aimmune Therapeutics, DBV Technologies, AnaptysBio, Adare Pharmaceuticals, and Stallergenes-Greer, has research sponsorship by Novartis, Sanofi, Astellas, Nestle, is a Data and Safety Monitoring Board member at Novartis and NHLBI, cofounded Before Brands, Alladapt, ForTra, and Iggenix; Chief Intellectual Office at FARE, Director of the World Allergy Organization (WAO) Center of Excellence at Stanford, Personal fees from Regeneron, Astrazeneca, ImmuneWorks, and Cour Pharmaceuticals, is a Consultant and Advisory Board Member at Ukko, Before Brands, Alladapt, IgGenix, Probio, Vedanta, Centecor, Seed, Novartis, NHLBI, EPA, National Scientific Committee of ITN and NIH Programs, and has filed US patents 62/647,389; 62/119,014; 12/610,940, 12/686,121, 10/064,936, 62/767,444 and S10-392; Dr Shifaa S Alkotob and Ms Melanie N Shojinaga report no COI.

⁸Department of Pediatrics, University of Colorado at Denver Health Sciences Center, Aurora, CO, USA

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atopic dermatitis; emollients; food allergy; transepidermal water loss; trilipid creams

To the Editor,

Allergic diseases are the most common chronic diseases in Westernized countries and bear substantial associated health and socio-economic burden. Atopic dermatitis (AD) affects approximately 20%–30% of infants,¹ while food allergy (FA) affects 5%–10% in early infancy. Approximately 40% of children with FA have experienced a severe, life-threatening allergic reaction and 40% report allergies to multiple foods.² Evidence shows early-onset AD (particularly within the first 3 months) to be associated with a markedly increased risk of FA at 12 months.³ Reducing both severity and duration of AD could potentially reduce the incidence of FA.⁴ Moreover, skin barrier was recently found to be defective (as determined by increased transepidermal water loss or TEWL, low filaggrin, and reduced long-chained lipid levels) in both lesional and nonlesional skin in children with FA, providing further evidence that skin barrier could be a target for prevention.^{5–7} There have been recent reports using paraffin-/petroleum-based, trilipid-based, or steroid-based emollients on infants to improve the skin barrier defect and thus potentially reduce FA.^{8,9} However, there is little evidence comparing emollients with each other in establishing improvement in TEWL.

We hypothesized that, in infants/children with dry skin/AD or FA, use of a trilipid cream would have greater efficacy in decreasing TEWL than a paraffin-based emollient. Emollients that are paraffin-based/alcohol-based/petroleum-based have variable effects and could possibly be detrimental to those with AD since occlusion inhibits keratinocyte differentiation and enhances *S aureus* colonization. In comparison, trilipid skin barrier creams have specific properties that lead to skin barrier restoration: a 3:1:1 ratio of ceramides, cholesterol, and free fatty acids, mimicking the skin's natural lipid composition, a low pH, similar to the physiological pH of skin, and free fatty acids that activate peroxisome proliferator-activated receptors (PPARs), which is reduced in AD.⁸ Unlike standard emollients, trilipid creams restore the normal lipid lamellar organization in the skin, enhance keratinocyte differentiation and function, as well as innate immune responses and reduce TEWL.

Therefore, we performed a pilot study in 45 infants/children with dry skin/AD to test whether use of Aveeno Daily Moisturizing Lotion (fragrance-free)TM vs EpiCeramTM improved TEWL (Table 1). The Aveeno is petrolatum-/paraffin-based with dimethicone (1.2%) being the active ingredient, pH 5.6. EpiCeram contains three essential lipids: ceramides, conjugated linoleic acid (CLA), and cholesterol in a physiologically balanced patented 3:1:1 ratio at a pH of 5. We recruited infants, toddlers, and children who had a doctor's diagnosis of dry skin or AD at one site (Stanford) under an IRB-approved protocol. Participants had no viral illnesses at the time of TEWL and were not on emollients or other medications. Participants and families were blinded, given the emollients in separate

containers, and instructions for storage at room temperature. They were taught how to apply the emollient evenly, what amount to use (a quarter size), and were instructed not to use other emollients over a 5-week period. Each participant served as a comparator (right vs left arm), and families were taught only to use one type of emollient on one arm vs contralateral arm. After emollients were wiped off 10 hours prior to the clinic visit, measurements of TEWL were taken using standardized procedures by trained study staff. TEWL was performed at baseline (either right or left arm-anterior surface of the forearm—the volar surface) and 5 weeks on nonlesional skin.

Results showed an improvement of skin barrier as measured by a reduction in TEWL (Figure 1). Infants and children (0–5 yrs) with dry skin/AD (n=45) were given EpiCeram daily (on left arm) vs Aveeno (on right arm) for 5 weeks, applied to lesional and nonlesional skin. A significant reduction in TEWL was observed ($p<0.001$) using a paired t test between 5 weeks vs baseline (Figure 1). In addition, using the same statistical analyses, we found a significant difference ($P<.001$) between right and left arm TEWL after 5 weeks of treatment with Aveeno vs EpiCeram. An intention-to-treat population was used for analysis. There were no dropouts. All individuals reported using the emollient for at least 5 out of 7 days. TEWL below 15 is considered normal. The same individuals are shown by connecting the lines between right and left arm.

The paired analyses assume (Figure 1) that the baseline measurement of contiguous pre-/postmeasurements would be equal to the baseline measurement of noncontiguous pre-/postmeasurements.

In conclusion, these preliminary results from a pilot, single site, blinded study show evidence of heterogeneity in TEWL response to different emollients. In this study, a trilipid cream was more effective than a paraffin-based emollient in reducing TEWL in those infants/children with known defects in the skin barrier. This has several implications as international studies are currently ongoing which attempt to test whether a specific emollient decreases FA risk; however, not all emollients seem to be the same in improving skin barrier defects (as measured by TEWL). To our knowledge, our study is the first to test one emollient vs another in TEWL outcomes. Our study is limited by several features since it used a small sample size, a single site, and patients only used the products for 5 weeks. In addition, participants were not randomized into separate groups but rather used as their own comparators, and mixing might have occurred in left vs right arm usage of emollient. Nevertheless, despite these limitations, our pilot data showed significant results. Further studies are underway to examine the effects of these two emollients on FA sensitivity.

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FIGURE 1.

Infants and children with dry skin or AD ($n = 45$) were given proactive care—EpiCeram daily (on left arm) vs reactive care—Aveeno as needed (on right arm) for 5 wk, applied to lesional and nonlesional skin. TEWL was performed on nonlesional skin as per published methods after creams were wiped off at least 10 h prior to TEWL. A significant reduction in TEWL was observed ($P < .001$) using a paired t test between right and left arm 5 wk of treatment with EpiCeram. TEWL below the reference black line of 15 is considered normal. Same individuals are shown by connecting lines between right and left arm

TABLE 1

Demographic information on 45 participants

Category	Outcome
Age range	4–82 mo
Time on emollient	5 wk
Sex	49% female
Food allergy alone (neither dry skin or AD)	33%
AD or dry skin alone (n = 3 with dry skin only by xerosis score)	33%
FA and AD (none with dry skin alone)	33%