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**Title: A randomised trial of a barrier lipid replacement strategy for the prevention of atopic dermatitis and allergic sensitisation: The PEBBLES Pilot Study**

**Running title: An RCT of barrier lipid replacement for prevention of AD**

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It is hypothesised that the impaired skin barrier in atopic dermatitis (AD) allows the immune system to be exposed to environmental allergens, resulting in sensitisation and allergic disease[1]. Two small trials recently found that routine use of emollients reduced the incidence of AD during the active treatment period by approximately half [2, 3]. It remains unknown if prophylactic use of emollients can prevent the development of AD beyond the treatment period (as opposed to simply delay its onset) or if this reduction in AD leads to a reduced risk of allergic sensitisation.

The previous trials in this area have used standard emollients[2, 3]. In this trial, we chose a ceramide dominant emollient (EpiCeram™), as it may provide greater preventive effects[4]. Skin affected by AD is deficient in ceramides [5]. EpiCeram has been formulated to contain physiological ratios of ceramides, cholesterol and free fatty acids, has a slightly acidic pH (5.0) which aids the production and secretion of ceramides by the skin[6]. Acidic emollients have been shown to help prevent AD and airway inflammation in a murine model. [7]. We

have previously demonstrated parent compliance, and initial evidence of safety, for use of EpiCeram for AD prevention in neonates[8].

We conducted a pilot randomised, parallel, single blind (outcome assessor), controlled trial of the effect of twice daily application of EpiCeram™ for the first six months of life on the incidence of AD and skin barrier function in high risk infants up to 12 months of age. Term infants with a family history of allergic disease were recruited from maternity wards (see online supplement). At enrolment, parents of infants in the intervention group were shownhow to apply approximately 6 grams of EpiCeram™ to the full skin surface of their child twice per day. Treatment was to commence within the first three weeks. No other skin care instructions were provided to either group.

Clinical follow-up of infants by a blinded assessor (CA) occurred at six weeks, six months and 12 months of age. Trans-epidermal water loss (TEWL), skin pH, hydration and "oiliness" (sebum) were assessed using standardized protocols (Courage & Khazaka, Cologne, Germany). At six and 12 months, skin prick tests were performed to six common allergens along with saline and histamine controls[9] (Stallergenes lancets; Hollister-Stier aero-allergen extracts, ALK (USA) food allergen extracts).

A total of 1306 infants were screened and 80 infants recruited (online Fig. 1). The groups were well balanced on a range of baseline factors (online table 1). There was minimal loss to follow-up at each time point (online Fig. 1).

There were no adverse reactions to the study cream. Adherence to the intervention was high (76% applied the cream for at least 5 days per week). Use of other emollients (not study treatment) on average for at least 3 days/week during the intervention period occurred in 39% of the control group and 18% of the intervention group (see online supplement).

Intention to treat analysis showed no significant effect of routine barrier lipid replacement in early life on AD or sensitisation outcomes (table 1). However, there was a trend towards reduced risks of AD and food sensitisation in the intervention group at six and 12 months of age (table 1, online table 3). Adjustment for slight baseline imbalances between groups (presence of siblings, forehead TEWL) did not materially alter the results (data not shown). Per protocol analyses (only including infants who received 5 days/week or more of study treatment) revealed a significant reduction in food sensitisation at 12 months in the treatment group (0% [0/21] versus 19.4% [7/36], p=0.04, online table 5). There were no differences between groups for bio-physical properties of the skin (online table 2). Among the

intervention group, children who developed food sensitisation had a later initiation of treatment (details in online supplement).

We found that twice daily prophylactic use of a ceramide dominant emollient, from the neonatal period to six months of age, was associated with a trend towards reduced incidence of AD and food sensitisation at age 12 months, suggesting that beneficial effects persisted for at least 6 months after stopping treatment. Whilst these results require confirmation, they support a role for skin barrier emollients in prevention of sensitisation and eczema beyond the treatment period. If barrier improvement interventions can prevent sensitisation and/or the development of chronic inflammatory processes in the skin that are found in adult AD, there may be long term preventive effects. Interestingly, we were unable to detect any effect of the intervention on skin barrier function(as measured by TEWL). While the effect size seen in this study for AD outcomes is similar to studies using standard emollients[2, 3], this is the first study to report outcomes beyond the treatment period or trends for reduced food sensitisation. Larger studies are required to examine the impact of such interventions on the development of other important outcomes, including food allergy and asthma. As EpiCeram™ is much more expensive than standard emollients, head to head studies and economic analysis would be required to demonstrate cost effectiveness. If such strategies are effective, they are likely to be incorporated into public health practice, as they are simple to implement and may help reduce the burden of these common conditions.



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**Table 1: Effect of intervention at six weeks, six and 12 months.**

| | Control group % (n/N) | Cream group % (n/N) | Risk ratio (95%CI) | P valu |
|---|---|---|---|---|
| UK working party definition | | | | |
| 6 weeks | 0% (0/38) | 7.7% (3/39) | - | 0.24 |
| 6 months | 18.9% (7/37) | 10.3% (4/39) | 0.54 (0.17- 1.70) | 0.34 |
| 12 months | 16.7% (6/36) | 8.1% (3/37) | 0.49 (0.13-1.80) | 0.31 |
| Cumulative to 6 months** | 21.6% (8/37) | 13.1% (5/38) | 0.61 (0.22-1.69) | 0.38 |
| Cumulative to 12 months** | 30.6% (11/36) | 18.4% (7/38) | 0.60 (0.26-1.38) | 0.28 |
| Investigator observed AD | | | | |
| 6 weeks | 0 (0/38) | 2.6 (1/39) | - | 1 |
| 6 months | 16.7 (6/36) | 10.26 (4/39) | 0.62 (0.19- 2.01) | 0.51 |
| 12 months | 16.2 (6/37) | 5.3 (2/38) | 0.32 (0.07-1.51) | 0.15 |
| Skin Prick tests | | | | |

| | | | | |
|---|---|---|---|---|
| Food allergens† | | | | |
| 6 months | 22.9% (8/35) | 12.8% (5/39) | 0.56(0.20- 1.56) | 0.20 |
| 12 months | 19.4% (7/36) | 8.8 (3/34) | 0.45 (0.13-1.61) | 0.31 |
| Inhalant allergens‡ | | | | |
| 6 months | 0% (0/35) | 0% (0/39) | - | 1 |
| 12 months | 2.8% (1/36) | 8.8 (3/34) | 3.18 (0.35-29.1) | 0.35 |
| Any allergen | | | | |
| Six months | 22.9% (8/35) | 12.8 (5/39) | 0.56 (0.20- 1.56) | 0.36 |
| 12 months | 22.2% (8/36) | 17.7 (6/34) | 0.79 (0.31-2.05) | 0.77 |

* Estimated using a Fisher's exact test.

** Combines responses from prior clinical assessments.

† Food allergens: egg white, cows' milk, peanut

‡ Inhalant allergens: dust mite, cat dander, and rye grass

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