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Skin barrier and cutaneous microbiota in the primary prevention of atopic dermatitis: current evidence and future perspectives

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ABSTRACT

Background. Atopic dermatitis (AD) is often the earliest manifestation of allergic multimorbidity in childhood. Epidermal barrier impairment and altered microbial colonization can be detected before overt disease, supporting a unified barrier-microbiota model of pathogenesis.

Aim. To examine the biological basis and clinical evidence for primary prevention of pediatric AD through interventions directed at skin barrier function, microbial ecology, or both.

Methods. Evidence from longitudinal cohorts, randomized trials, systematic reviews, meta-analyses, and international guidance was appraised narratively, with emphasis on pediatric populations and clinically diagnosed AD.

Main findings. Current evidence highlights a complex and evolving preventive landscape. While large pragmatic trials have not demonstrated a consistent benefit of routine neonatal emollient use, emerging data suggest that timing, formulation, and biological risk stratification may influence preventive efficacy. Microbiota-directed strategies, especially selected probiotic interventions, have shown promising but strain- and timing-dependent effects, supporting further investigation of integrated barrier- and microbiota-based approaches.

Conclusions. Infant skincare should not be presented as proven AD prevention. Future trials should enroll biologically defined risk groups, target prespecified windows, integrate barrier and microbial biomarkers, and use harmonized outcomes.

KEYWORDS: Atopic dermatitis, skin barrier, cutaneous microbiota, primary prevention, infant

1. INTRODUCTION

Atopic dermatitis (AD) is the most common chronic inflammatory skin disorder of childhood, affecting approximately 10-20% of children in many populations, although estimates vary with geography, age, and case definition [1]. In addition to itch, sleep disruption, infection, and

family burden, early and persistent AD is associated with food allergy, asthma, and allergic rhinitis. This progression is heterogeneous rather than inevitable; the term 'atopic march' should therefore be understood as a set of partly overlapping trajectories, not a fixed sequence [2-5].

The skin is central to these trajectories. Genetic and acquired defects in epidermal differentiation increase transepidermal water loss (TEWL), alter surface pH and lipid composition, and facilitate penetration of irritants, microbes, and allergens. In parallel, early-life microbial communities influence epithelial maturation and immune tolerance. Barrier dysfunction and dysbiosis may therefore be mutually reinforcing processes rather than competing explanations for AD [6-9]. This integrated view provides a compelling rationale for prevention, but biological plausibility has not consistently translated into clinical efficacy.

This narrative review critically evaluates the barrier-microbiota axis in the primary prevention of pediatric AD. It distinguishes prevention of incident disease from treatment of established AD, separates clinical outcomes from surrogate biomarkers, and translates the evidence into practical counselling and research priorities.

2. MATERIALS AND METHODS

A targeted narrative search of PubMed/MEDLINE was updated through July 2026. Search concepts covered AD, infant skin barrier, filaggrin, TEWL, epidermal lipids, cutaneous and intestinal microbiota, *Staphylococcus aureus,* emollients, skincare, probiotics, prebiotics, synbiotics, live biotherapeutic products, food allergy, and primary prevention. Priority was given to longitudinal birth cohorts, randomized controlled trials, systematic reviews, meta-analyses, international guidance, and studies with pediatric or early-life relevance. Reference lists of key publications were examined to identify additional studies.

Evidence was appraised narratively according to population risk, intervention timing and formulation, adherence, comparator, AD definition, duration of follow-up, and distinction between clinical disease and surrogate outcomes. Because the objective was interpretive synthesis rather than exhaustive evidence retrieval, no formal risk-of-bias tool, protocol registration, or pooled quantitative analysis was undertaken.

For interpretation, primary prevention was defined as intervention before clinically diagnosed AD. Studies enrolling children with established eczema were considered only when they clarified mechanism, safety, or future preventive development and were not treated as direct evidence of prevention. Greater weight was given to adequately powered randomized trials with blinded outcome assessment and post-intervention follow-up than to uncontrolled studies, secondary subgroup findings, or changes in laboratory markers alone.

3. THE EARLY-LIFE SKIN BARRIER AS A DETERMINANT OF AD RISK

The stratum corneum consists of corneocytes embedded in a matrix of ceramides, cholesterol, and free fatty acids. In a secondary analysis of 116 high-risk infants, TEWL measured during the first week predicted subsequent AD independently of filaggrin (FLG) status, whereas hydration and surface pH were less informative [10]. More recent neonatal data found that high TEWL within 48 hours was associated with AD by 3 months (adjusted HR 3.31, 95% CI 1.47-7.44; p=0.004) [11], supporting barrier function as a risk marker rather than a diagnosis.

Filaggrin degradation products contribute to natural moisturizing factor, hydration, and acidic surface pH. FLG loss-of-function variants are among the strongest and most consistently replicated genetic risk factors for AD in populations of European ancestry [12-14], but incomplete penetrance, ancestry-specific variation, and inflammation-induced suppression of barrier proteins preclude a single-gene model.

Figure 1 summarizes the proposed barrier-microbiota-immune interaction and identifies which preventive approaches remain investigational (Fig. 1).

AD-prone skin can show shorter ceramide and free-fatty-acid chains and altered lamellar organization [15,16]. Because products differ in lipids, vehicle, dose, and timing, 'emollient' is not a biologically uniform intervention.

4. CUTANEOUS MICROBIOTA: PARTNER AND AMPLIFIER OF BARRIER DYSFUNCTION

Infant skin develops site-specific microbial communities during the first year. Delivery mode, gestational age, contacts, antibiotics, climate, and skincare influence composition, while marked interpersonal variation limits any single 'healthy' profile [7,17,18]. Longitudinal sampling is essential to establish temporality.

Reduced diversity and expansion of *Staphylococcus aureus* accompany active AD, but longitudinal findings are not uniform. In the Kennedy birth cohort, commensal staphylococci at 2 months were significantly less abundant among infants who developed AD by 12 months [7]; importantly, *S. aureus* was not consistently detected before onset in that cohort. Other longitudinal studies reported that *S. aureus* colonization preceded diagnosis [19]. These apparently discordant observations reflect site, age, strain, sampling, and case-definition differences and argue against treating one taxon as a universal predictive biomarker [7,19,20].

Reduced natural moisturizing factor and higher pH can favor *S. aureus,* while microbial inflammation disrupts junctions and lipids. Microbiome shifts are surrogate outcomes and cannot demonstrate prevention without fewer clinically diagnosed AD cases. Gut–skin associations are likewise heterogeneous and not directly actionable [21]. Swab sequencing measures relative DNA abundance, and not

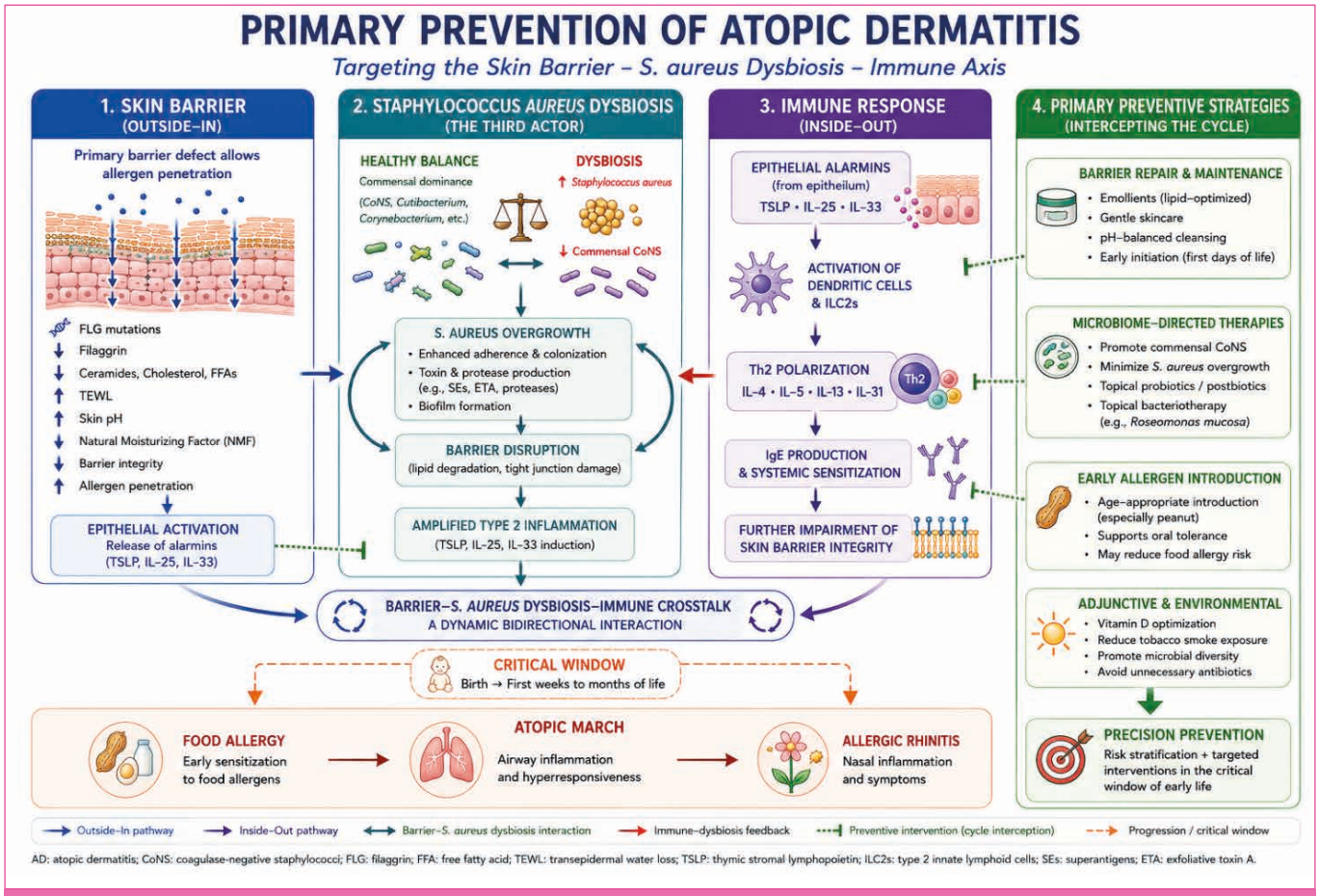


FIGURE 1. Proposed barrier–S. aureus dysbiosis–immune axis in the primary prevention of atopic dermatitis. The right-hand interventions represent biological hypotheses or research priorities; only early allergen introduction has robust evidence for prevention of selected food-allergy outcomes, whereas routine emollients and microbiome-directed products are not established primary prevention of AD.

necessarily viability or strain-level function. Sampling site, bathing, topical treatment, antibiotics, storage, extraction, and analytic pipeline alter results. Cohorts therefore require standardized longitudinal sampling and paired barrier measurements [7,9,17,18].

5. BARRIER-DIRECTED PRIMARY PREVENTION

Barrier-directed prevention is based on a simple biological premise: if epidermal barrier dysfunction is an early event in the atopic march, then strengthening the skin before eczema becomes clinically apparent might reduce the risk of disease onset. The earliest randomized data were encouraging. In the Japanese trial by Horimukai et al., 118 high-risk neonates were randomized 1:1 to daily application of an emulsion-type moisturizer for the first 32 weeks of life or to usual care. By week 32, the moisturizer arm showed an approximately 32% relative reduction in AD/eczema compared with the control arm (p=0.012). The study did not show a significant effect on allergic sensitization, but sensitization was more common in infants who developed AD/eczema, supporting the idea that barrier failure and early inflammatory skin disease are closely linked [22]. In the feasibility trial by Simpson et al., 124 high-risk neonates in the US and UK were assigned to daily full-body emollient use started within 3 weeks of birth or to no regular emollient. The intervention was acceptable to families, no emollient-related adverse events were observed, and the cumulative incidence of AD at 6 months was reduced by about 50% (RR 0.50, 95% CI 0.28-0.90; p=0.017) [23]. These two pilot studies were important because they suggested that very early barrier reinforcement could be preventive, although they were small, short-term, and not definitive.

That initial signal was not reproduced consistently in larger pragmatic trials. In BEEP, 1,394 term infants with a family history of atopic disease were randomized to daily emollient application during the first year

of life plus standard advice or to standard advice alone. At 2 years, eczema was present in 23% of infants in the emollient group versus 25% in controls (adjusted RR 0.95, 95% CI 0.78-1.16; p=0.61), and the mean number of skin infections in year 1 was higher with emollient use (0.23 *vs*. 0.15 per child; adjusted incidence rate ratio 1.55, 95% CI 1.15-2.09) [24]. Longer follow-up remained negative: at age 5 years, parent-reported doctor-diagnosed AD between 12 and 60 months was reported in 31% of the emollient group versus 28% of controls (adjusted RR 1.10, 95% CI 0.93-1.30), with no reduction in food allergy, asthma, or hay fever [25]. In the population-based PreventADALL trial, the skin arm used bath emollients and facial cream from 2 weeks of age to less than 9 months, at least four times per week, although the intervention did not show a meaningful preventive effect on AD in subsequent analyses [26]. By contrast, STOP-AD suggested that timing and intensity may be relevant: in 321 high-risk infants recruited within 4 days of birth, twice-daily emollient use for 8 weeks reduced AD at 12 months from 46.4% to 32.8% (RR 0.707, 95% CI 0.516-0.967; p=0.036) [27]. This positive result is important, but it comes from a single-center study and should be interpreted cautiously until it is replicated.

The most robust overall synthesis supports caution rather than routine prophylaxis. The Cochrane individual-participant-data review identified 33 randomized trials involving 25,827 babies, but only a minority contributed sufficiently comparable data for pooled analysis. Across 7 studies and 3,075 infants, skincare interventions probably did not reduce eczema by age 1-3 years (RR 1.03, 95% CI 0.81-1.31), and across 6 studies and 2,728 infants they probably increased local skin infections (RR 1.34, 95% CI 1.02-1.77) [28].

Head-to-head randomized trials comparing different emollient formulations for primary prevention of AD are lacking, and the formulations tested across prevention trials varied considerably in composition [29]. In their systematic review of prevention RCTs, Grześk-Kaczyńska et al. concluded that the evidence remains ambiguous and that it is still unclear which composition might be of the greatest benefit for AD prophylaxis[29]. Similarly, in the therapeutic setting, no moisturiser has generally been shown to be superior to another, although many proprietary products claim to target AD pathophysiology without rigorous evaluation[30]. Therefore, rather than recommending specific brands, we suggest that clinicians advise parents on formulation attributes. For infant skincare products, the European Roundtable recommendations support formulations buffered at approximately pH 5.5 to preserve the skin's acid mantle, effectively preserved, free of harsh surfactants such as sodium lauryl sulfate, and supported by appropriate safety testing[31]. In addition, particularly in young children, products should preferably be free of protein allergens and of common contact haptens associated with allergic contact dermatitis, such as lanolin and methylisothiazolinone[31].

With regards to product selection, no study has demonstrated that oat- or rice-containing rinse-off cleansers cause food sensitization in healthy infants. The available evidence is limited and derives mainly from children with established AD and from leave-on or experimental topical exposures rather than from routine cleansing. In children with AD, the use of oat-containing emollients has been associated with oat sensitization, although causality has not been established[32]. Conversely, a double-blind patch-test study found no evidence of allergic sensitization to topical colloidal oat or rice preparations in young children, although irritant reactions were observed in a minority of atopic children[33]. Evidence concerning rice-derived ingredients is particularly limited, with a pediatric case report describing rice-bran allergy following occupational-type environmental exposure in a family rice shop and suggesting a possible role for percutaneous sensitization, rather than demonstrating a risk associated with cosmetic use [34]. Therefore, oat- or rice-derived proteins should not be considered an established contraindication in infant cleansers. Nevertheless, given the biological plausibility of epicutaneous sensitization and the absence of a demonstrated preventive benefit from adding dietary proteins to infant skincare products, protein-free formulations may reasonably be preferred as a precaution, particularly for infants with established AD or markedly inflamed skin [32-34].

6. MICROBIOTA-DIRECTED AND ENVIRONMENTAL STRATEGIES

Microbiota-directed primary prevention has been tested across prenatal-only, maternal-perinatal, combined maternal-infant, and infant-only schedules, but the signal is clearly strain- and timing-dependent rather than class-wide [35–37]. Prenatal-only *Lactobacillus rhamnosus* GG (LGG) did not prevent eczema (RR 0.88, 95% CI 0.63-1.22) [38]. By contrast, the combined maternal–infant HN001 regimen, given to mothers from late pregnancy and then to infants from birth, produced a durable reduction in eczema: in follow-up, HN001 remained associated with lower cumulative eczema risk (HR 0.56, 95% CI 0.39-0.80), whereas HN019, tested in the same trial framework, had no significant effect [39]. Maternal-only HN001 later failed to reproduce the benefit, underscoring that timing and infant exposure are important [40]. Maternal prebiotics were also negative (adjusted RR 0.98, 95% CI 0.77-1.23) [41].

The individual randomized trials show the same pattern of heterogeneity [38,39,42,43]. In the Norwegian probiotic-milk trial, women received probiotic milk containing LGG, *L. acidophilus* La-5, and *Bifidobacterium animalis* subsp. lactis Bb-12 from 36 weeks of gestation until 3 months postpartum while breastfeeding; at 2 years, cumulative AD was reduced (OR 0.51, 95% CI 0.30-0.87; p=0.013) [44]. In the Korean trial, 112 pregnant women at hereditary risk received a daily mixture of *Bifidobacterium bifidum*, *B. lactis*, and *L. acidophilus* from 4-8 weeks before delivery until 6 months postpartum; eczema at 1 year was 18.2% *vs*. 40.0%, and cumulative eczema during the first year was 36.4% *vs*. 62.9% [45]. In contrast, the Japanese 2 x 2 newborn study combining skin care and synbiotics found no preventive effect for either intervention, with 459 infants assessable at 1 year [43]. Among later infant-focused probiotic studies, a multistrain high-dose regimen from 36 weeks of gestation to 6 months postnatally did not reduce diagnosed eczema at 2 years (34.1% *vs*. 32.4%), although secondary outcomes favored the active arm for sensitization and

atopic eczema [46]. *Lactobacillus reuteri* likewise failed to reduce overall eczema in a high-risk family study, but IgE-associated eczema and some sensitization outcomes were lower [47]. LGG given from 4-6 weeks before delivery through 6 months postpartum was null and was associated with more recurrent wheezy bronchitis [48]. An infant-only LGG trial also found no reduction in eczema at 2 years (HR 0.95, 95% CI 0.59-1.53) [49]. Later infancy studies were again mixed: *Lactobacillus* F19 reduced eczema at 13 months (11% *vs*. 22%; NNT 9) [50], and a late-infancy mixture of *Lactobacillus rhamnosus* and *Bifidobacterium animalis* subsp. lactis lowered eczema incidence before day-care attendance (4.2% *vs*. 11.5%) [51]. Preliminary maternal *Bifidobacterium bifidum* PRL2010 data did not show a statistically robust preventive effect; only 41 children completed the 12-month assessment, and the absence of attributed adverse events does not establish safety in a study of this size [52]. A 2026 trial in 360 formula-fed children younger than 3 years reported a markedly lower eczema incidence with *Bifidobacterium animalis* subsp. lactis BLa80 than with placebo, but the broad age range, unusually large effect, and single-study status require cautious interpretation and independent replication [53]. Taken together, trial-level evidence suggests that any preventive benefit is specific to selected strain-schedule combinations and should not be treated as a probiotic class effect [35–37].

Prebiotic trials have been less consistent. Early formula supplementation with galacto- and fructo-oligosaccharides reduced AD during the first 6 months of life in high-risk, formula-fed infants (9.8% *vs*. 23.1%) [54]. Later prebiotic-enriched formula trials were negative, including the prebiotic-supplemented partially hydrolyzed formula study, in which eczema by 12 months was 28.7% in both arms [55]. More recently, maternal prebiotic supplementation during pregnancy and lactation also failed to reduce medically diagnosed eczema by age 1 year [41]. Pooled analyses mirror this heterogeneity: in a 28-study meta-analysis, only combined prenatal–postnatal administration was clearly favorable (OR 0.67, 95% CI 0.54-0.82), whereas prenatal-only or postnatal-only schedules were not clearly effective [35]. A 2025 umbrella analysis reported a pooled reduction in AD incidence (RR 0.74, 95% CI 0.70-0.79) across prevention syntheses; its separate reduction in SCORAD (WMD -.75, 95% CI -5.08 to -2.42) concerned treatment of established disease and should not be interpreted as prevention [36]. Major strain, timing, population, and outcome heterogeneity limits clinical generalization. Accordingly, the WAO guidance remains conditional and based on very low-certainty evidence, and does not support universal routine supplementation as a standard preventive strategy [37].

Microbiota-directed topical approaches should be interpreted as treatment studies rather than true primary prevention. In a first-in-human work, topical *Roseomonas mucosa* was tested in 10 adults and 5 children with established AD and was associated with reduced disease severity, lower topical steroid use, and lower *S. aureus* burden, but this was an open-label safety/activity study and cannot be extrapolated to healthy neonates [56,57]. The subsequent randomized FB-401 trial in 154 participants aged 2 years and older with mild-to-moderate AD did not meet its primary endpoint [58]. Likewise, the SWET trial of ion-exchange water softeners in 336 children with moderate-to-severe eczema in hard-water areas showed no objective blinded clinical benefit and did not justify routine use as prevention [59].

More broadly, the observed associations between eczema and pet exposure [60,61] or biodiversity-related exposures [62] are useful for hypothesis generation, but they are observational and vulnerable to confounding. Together with healthy-infant skincare recommendations [31], these observations do not justify deliberate microbial exposure, antiseptic bathing, topical antibiotic prophylaxis, or household decolonization as AD-prevention strategies in healthy neonates (Tab. I). This is a cautious clinical inference rather than evidence that such interventions have been tested for primary prevention. The practical implication is that microbiota-based prevention remains biologically plausible but not yet ready for broad routine use outside rigorously designed, strain-specific, high-risk protocols.

7. INTEGRATING BARRIER AND MICROBIOTA IN PRECISION PREVENTION

The central lesson from prevention trials is that population selection and biological timing are relevant. Family history is readily available but nonspecific. FLG genotype captures one pathway, while neonatal TEWL measures function across genetic and environmental influences [10,12]. Skin-surface lipids, natural moisturizing factor, cytokines, and microbial features may add information, but candidate panels require external validation and demonstration that biomarker-guided intervention improves outcomes [64–66]. Pediatric biomarker frameworks further emphasize that no single marker currently has sufficient validation for routine prediction or treatment selection [66]. Prospective cohort data support this enrichment role: forehead TEWL measured in the first week of life predicted later AD regardless of FLG mutation status, with an optimal cutoff of 6.5 g/m^2/h [10].

Precision-prevention trials should prespecify risk strata, intervene before clinical inflammation, characterize formulation or microbial function, and assess AD after treatment is stopped. Combined approaches require factorial or adaptive testing rather than mechanistic inference.

The barrier model also clarifies the relationship with food allergy. The dual-allergen-exposure hypothesis proposes that exposure through inflamed skin promotes sensitization, whereas timely oral exposure promotes tolerance [67]. Randomized evidence supports early peanut introduction in appropriately assessed infants at increased risk [68]. This is prevention of food allergy, not proof that feeding prevents AD, and advice should follow current age-, safety-, and country-specific guidance. Prompt control of established eczema is clinically important, but whether it modifies the entire atopic trajectory remains unresolved.

Universal FLG sequencing is limited by ancestry-specific variants and incomplete penetrance. TEWL varies with instrument, site, humidity,

TABLE I. Principal barrier- and microbiota-directed studies.

Study/design	Population and intervention	Main result
Horimukai et al., 2014; pilot RCT [22]	118 high-risk neonates; daily emulsion for 32 weeks.	118 high-risk neonates (59 intervention, 59 control); daily emulsion from birth to 32 weeks. AD/eczema was reduced by about 32% (p=0.012); allergic sensitization was not significantly reduced.
Simpson et al., 2014; pilot RCT [23]	124 high-risk neonates; full-body emollient at least once daily starting within 3 weeks of birth for 6 months.	124 randomized (60 control, 64 intervention); cumulative AD at 6 months was 43% *vs.* 22% (RR 0.50, 95% CI 0.28-0.90; p=0.017); no emollient-related adverse events were reported.
BEEP, 2020 and 2023 follow-up; multicentre RCT [24,25]	1,394 high-risk infants; daily emollient through age 1 year.	At 2 years, eczema was 23% *vs.* 25% (adjusted RR 0.95, 95% CI 0.78-1.16; p=0.61), and skin infections in year 1 were more frequent with emollient use. At 5 years, parent-reported doctor-diagnosed AD was 31% *vs.* 28% (adjusted RR 1.10, 95% CI 0.93-1.30), with no reduction in food allergy, asthma, or hay fever.
PreventADALL, 2020; factorial RCT [26]	2,397 newborns; skin intervention from 2 weeks and/or early food introduction.	2,397 newborns from a general population; skin emollients from 2 weeks of age. AD at 12 months was 48/596 (8%) in the no-intervention group and 64/575 (11%) in the skin-intervention group (risk difference 3.1%, 95% CI -0.3 to 6.5). No safety concerns were identified.
STOP-AD, 2023; RCT [27]	321 high-risk infants; emollient twice daily from birth to 8 weeks.	321 high-risk infants randomized within 4 days of birth to 8 weeks of specialized emollient. AD at 12 months was 32.8% *vs.* 46.4% (RR 0.707, 95% CI 0.516-0.965; p=.036); skin infections during the intervention period were 5.0% *vs.* 5.7%.
Kelleher et al., 2022; Cochrane review [28]	33 trials; 25,827 participants; infant skin-care interventions.	33 trials, 25,827 participants. No reduction in eczema at 1-3 years (RR 1.03, 95% CI 0.81-1.31); local skin infections increased (RR 1.34, 95% CI 1.02-1.77).
Kalliomäki et al., 2001 RCT and 2003 follow-up [42,63]	High-risk dyads; LGG before delivery, then mother or infant for 6 months.	At 2 years, AD occurred in 15/64 (23%) infants in the probiotic group *vs.* 31/68 (46%) in placebo (p=.008). The separate 4-year follow-up of the same cohort reported atopic eczema in 14/53 *vs.* 25/54 (RR 0.57, 95% CI 0.33-0.97).
Boyle et al., 2011; prenatal-only RCT [38]	250 high-risk pregnancies; maternal LGG from 36 weeks to delivery.	250 high-risk pregnancies; maternal LGG from 36 weeks to delivery. Eczema was 34% *vs.* 39% (RR 0.88, 95% CI 0.63-1.22); IgE-associated eczema was 18% *vs.* 19% (RR 0.94, 95% CI 0.53-1.68).
ProPACT, 2010; maternal perinatal RCT [44]	Non-selected mothers; probiotic milk from 36 weeks to 3 months postpartum while breastfeeding.	415 pregnant women randomized to probiotic milk or placebo. At 2 years, cumulative AD was lower in the probiotic group (OR 0.51, 95% CI 0.30-0.87; p=0.013); there was no significant effect on asthma or sensitization.
Wickens et al., 2013; maternal-infant RCT follow-up [39]	HN001 or HN019 from late pregnancy; infants supplemented to age 2 years.	Maternal HN001/HN019 from late pregnancy and infant supplementation showed a strain-specific effect. HN001 reduced cumulative eczema through 6 years (HR 0.56, 95% CI 0.39-0.80) and SPT sensitization (HR 0.69, 95% CI 0.48-0.99); HN019 had no significant effect.
Dissanayake et al., 2019; factorial RCT [43]	Newborns; skincare and/or synbiotic intervention.	459 babies were assessable at 1 year. Neither emollient nor synbiotic, alone or in combination, reduced AD or food allergy.
Moro et al., 2006; prebiotic RCT [54]	259 high-risk formula-fed infants; GOS/FOS mixture.	259 high-risk formula-fed infants; 102 in the prebiotic group and 104 in the placebo group completed the study. AD developed in 9.8% *vs.* 23.1%, and fecal bifidobacteria increased with prebiotic supplementation.
Li et al., 2019; meta-analysis [35]	28 prenatal and/or postnatal probiotic studies.	28 randomized studies: combined prenatal-postnatal probiotic administration reduced AD risk (OR 0.67, 95% CI 0.54-0.82), whereas isolated schedules were less consistent.
Probiotic umbrella review, 2025 [36]	Meta-analyses of prenatal and/or infant probiotic supplementation.	38 meta-analyses including 127,150 participants. Prevention syntheses showed lower AD incidence (RR 0.74, 95% CI 0.70-0.79); the SCORAD reduction (WMD -3.75, 95% CI -5.08 to -2.42) derived from treatment syntheses. Heterogeneity was high.
PRL2010, 2025; maternal RCT [52]	Atopic mothers; *Bifidobacterium bifidum* PRL2010 from 36 weeks through breastfeeding.	Only 41 children completed the 12-month assessment. AD occurred in 1/24 *vs.* 2/17 (p=.37); no attributed adverse events were reported, but the study was too small to establish preventive efficacy or safety.

(continues)

TABLE I (*follows*). Principal barrier- and microbiota-directed studies.

Study/design	Population and intervention	Main result
PATCH, 2016; infant formula RCT [55]	863 high-risk infants; prebiotic-supplemented partially hydrolyzed formula.	863 high-risk infants randomized to prebiotic-supplemented partially hydrolyzed formula or control. Eczema by 12 months was 28.7% *vs.* 28.7% (OR 0.98, 95% CI 0.68-1.40; p=.90); no meaningful prevention signal emerged.
Allen et al., 2014; perinatal RCT [46]	Pregnant women and infants; high-dose four-strain probiotic through 6 months.	High-dose 4-strain probiotic from 36 weeks gestation to 6 months after birth. Primary eczema was 34.1% *vs.* 32.4% (OR 1.07, 95% CI 0.72-1.60), but atopic eczema was lower (5.3% *vs.* 12.1%; OR 0.40, 95% CI 0.18-0.91) and sensitization also fell (10.5% *vs.* 18.5%).
Kim et al., 2010; maternal-infant RCT [45]	112 high-risk pregnancies; three-strain mixture before and after birth.	112 high-risk pregnancies; only 68 infants completed follow-up. Cumulative eczema was 36.4% *vs.* 62.9% (p=0.029), but attrition was substantial.
Abrahamsson et al., 2007; perinatal RCT [47]	232 high-risk families; *L. reuteri* from gestational week 36 and to infants for 12 months.	232 families, 188 completed. Overall eczema was 36% *vs.* 34%, but IgE-associated eczema was 8% *vs.* 20% (p=0.02); skin-prick reactivity was lower in infants of mothers with allergy.
Kopp et al., 2008; perinatal RCT [48]	105 high-risk pregnancies; LGG before delivery and during infancy.	105 high-risk pregnancies, 94 families completed. Eczema was 28.0% *vs.* 27.3% (RR 0.96, 95% CI 0.38-2.33); recurrent wheezing bronchitis was more frequent in the LGG group.
Palmer et al., 2025; maternal prebiotic RCT [41]	652 high-risk pregnancies; prebiotics during pregnancy and lactation.	652 high-risk pregnancies. Maternal prebiotics from early pregnancy through lactation did not reduce infant eczema: 31.5% *vs.* 32.6% (adjusted RR 0.98, 95% CI 0.77-1.23; p=.84).
TIPS, 2017; infant-only RCT [49]	High-risk infants; LGG during the first 6 months of life.	203 infants were randomized and 184 initiated treatment. Eczema at 2 years was 30.9% in controls and 28.7% with LGG (HR 0.95, 95% CI 0.59-1.53), so the primary prevention claim was not supported.
West et al., 2009; weaning RCT [50]	179 infants; Lactobacillus F19 in cereal from age 4 to 13 months.	179 infants received cereals with or without *Lactobacillus* F19 from 4 to 13 months. Eczema at 13 months was 11% *vs.* 22% (p<0.05; NNT 9), with a higher IFN-gamma/IL4 ratio in the probiotic group.
Schmidt et al., 2019; late-infancy RCT [51]	Probiotic mixture before day-care attendance for 6 months.	290 participants randomized before day-care attendance. Eczema at follow-up was 4.2% *vs.* 11.5% (p=.036); asthma, rhinitis, conjunctivitis and sensitization were unchanged.
BLa80, 2026; infant/child RCT [53]	360 formula-fed children aged <3 years at increased allergy risk; 180-day supplementation with *Bifidobacterium animalis* subsp. lactis BLa80.	Eczema incidence was 27.6% *vs.* 69.5% (RR 0.398; p<.001). The broad age range, unusually large effect, and single-study status require cautious interpretation and independent replication.
FB-401, 2024; phase II RCT [58]	Patients aged ≥2 years with mild-to-moderate AD; topical *Roseomonas mucosa* formulation.	154 participants aged 2 years or older with mild-to-moderate AD were randomized 1:1 to FB-401 or placebo. The primary efficacy endpoint was not met, so the study is indirect for primary prevention.
SWET, 2011; treatment RCT [59]	Children with established moderate-to-severe eczema; domestic ion-exchange water softener.	336 children aged 6 months to 16 years with moderate/severe eczema lived in hard-water areas. The mean SASSAD change at 12 weeks was -5.0 *vs.* -5.7 (mean difference 0.66, 95% CI -1.37 to 2.69; p=0.53), so the intervention was not clinically useful.

acclimatization, and behavior. Any model must improve prediction beyond family history and link to an intervention with a favorable benefit–harm balance.

8. PRACTICAL IMPLICATIONS FOR PEDIATRIC CARE

Clinicians should explain that no routine emollient or skincare regimen has yet been shown to prevent AD reliably in all infants. Routine daily emollients should not be promoted as a proven preventive intervention, although moisturizers should be used appropriately when xerosis or eczema is present. In infants with cutaneous xerosis or recurrent scaly patches in the absence of clinically established atopic dermatitis, emollients may be used as first-line treatment to restore and maintain skin hydration and barrier function [30,31]. Their use need not be limited to the acute phase until visible resolution; regular application may be continued while xerosis persists or recurs, with the frequency adjusted

according to the infant's skin condition, clinical response, and tolerance [30,31]. Once the skin has remained normal, application can be reduced or reserved for areas and periods of recurrent dryness. Persistent, recurrent, or inflammatory lesions – particularly when associated with erythema, pruritus, excoriation, exudation, or poor response – should prompt clinical reassessment to confirm the diagnosis and determine whether additional anti-inflammatory treatment is required. This therapeutic use of emollients should be distinguished from routine prophylactic use in healthy infants and should not be interpreted as evidence that emollients reliably prevent the development of atopic dermatitis [24,28]. Families can be advised to use simple, fragrance-free skincare and avoid irritant practices without promising disease prevention. These cautions are particularly important for prophylactic emollients: in BEEP, daily emollient use during the first year did not reduce eczema at 2 years (23% *vs*. 25%; adjusted RR 0.95, 95% CI 0.78-1.16) and was associated with more skin infections (0.23 *vs*. 0.15 per child; adjusted incidence rate ratio 1.55, 95% CI 1.15-2.09) [24]; at 5 years, cumulative AD remained similar (31% *vs*. 28%; adjusted RR 1.10, 95% CI 0.93-1.30) [25]. The Cochrane individual-participant review likewise found no eczema prevention at 1-3 years (RR 1.03, 95% CI 0.81-1.31) but more local skin infections (RR 1.34, 95% CI 1.02-1.77) [28]. Breastfeeding should be supported for its established health benefits, and not framed as guaranteed AD prevention. Maternal dietary restriction during pregnancy or lactation should not be recommended solely to prevent eczema. Probiotic or prebiotic products should not be prescribed as interchangeable preparations [36,37], and topical bacteriotherapy should remain within research protocols [56–58]. Infants who develop eczema require timely diagnosis, severity assessment, effective anti-inflammatory treatment, infection management when indicated, and evidence-based counselling about introduction of allergenic foods [66,67].

9. RESEARCH PRIORITIES

Future studies should use validated AD criteria, report onset and severity separately, adopt the HOME core outcome set [69], and continue follow-up beyond the intervention period. Trials should document adherence, co-interventions, adverse skin events, product composition, and contamination with environmental food proteins. Mechanistic outcomes such as TEWL or microbial diversity should complement, not replace, clinically diagnosed AD. Future studies should also prespecify absolute risk differences, adverse-event definitions, and post-intervention durability of effect, because safety and persistence are as relevant as point efficacy in this field [24,28].

Priority questions include whether ultra-early lipid-targeted formulations benefit infants with demonstrable barrier impairment; whether microbial functions predict disease more reproducibly than taxonomic abundance; whether live biotherapeutics can be used safely before disease onset; and whether integrated biomarker algorithms provide sufficient incremental value to justify screening. Prespecified subgroup analyses and adequately powered interaction tests are essential to avoid converting chance findings into clinical recommendations.

10. CONCLUSIONS

Epidermal barrier dysfunction and microbial dysbiosis may form a mutually reinforcing early-life axis that helps explain the onset of pediatric AD and its relationship with allergic sensitization [6,7,10,12]. The model is biologically coherent, but current preventive evidence does not support routine prophylactic emollients or microbiota-directed products for all infants [24,28,36,37]. Gentle skincare is appropriate for general skin health, while proven treatment should begin promptly when AD develops [24,28,31]. Accordingly, the most defensible current message is biologically informed risk enrichment, not universal prophylaxis: no biomarker or routine topical regimen is yet ready for stand-alone screening or routine use in all healthy neonates [10,12,64,66].

The next phase of research should replace uniform intervention with prospectively tested precision prevention: biologically defined risk, a clearly timed and characterized intervention, standardized clinical outcomes, and long-term safety assessment [68]. Early biologic treatment of established pediatric AD has generated interest as a potential secondary-prevention strategy, but current publications describe treatment rather than demonstrating prevention of the atopic march; these data should not be extrapolated to primary prevention [70,71]. Until appropriately designed longitudinal trials are available, transparent communication of uncertainty is as important as enthusiasm for the barrier-microbiota paradigm.

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Conflicts of interest statement

The authors declare no conflicts of interest.

Author's contributions

Conceptualization, C.I. and S.C.; methodology, A.K., S.C. and C.I.; investigation, A.K., C.I., S.C.; writing-original draft preparation, A.K., C.I., S.C.; writing-review and editing, C.G.; M.M.d.G and G.L.M; supervision, V.C., C.F., F.G., A.L., S.M., A.A.S., G.M., M.M.d.G., G.L.M.; review and editing V.C., C.F., F.G., A.L., S.M., A.A.S., G.M., M.M.d.G., G.L.M.; visualization, A.K. and C.I.; project administration, A.K., C.I. and S.C. All authors have read and agreed to the published version of the manuscript.

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