Research Article

Disease Modification in Pediatric Atopic Dermatitis: An Integrative Model Combining Targeted And Natural Therapies

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Abstract

Atopic dermatitis (AD) is the most common chronic inflammatory skin disease of childhood, and the goal of its treatment is shifting from suppressing flares to altering the disease trajectory. This narrative review, based on a non-systematic PubMed search prioritizing 2021-2026 publications, examines how well this shift is supported by evidence and what stands in the way of its implementation in pediatric practice. Longitudinal cohorts show that only a minority of children follow the classic atopic march. Early intervention should therefore target high-risk phenotypes rather than the diagnosis. Large randomized trials did not confirm that emollients applied from birth prevent AD. Among targeted agents, dupilumab has the most data: in retrospective cohorts it is associated with a lower risk of new atopic comorbidities, and some children remain in remission after withdrawal. These data are observational, and the 2026 consensus definitions of remission have not been validated in children. Adjunctive natural therapies, such as climatotherapy and balneotherapy, act on the skin barrier, the microbiome and itch, but their evidence base is dated, heterogeneous and largely non-randomized. We propose an integrative model in which targeted therapy induces disease control and structured adjunctive programs support barrier recovery during de-escalation. We present it as a testable hypothesis and an organizational innovation, not a clinical recommendation. Its implementation is limited by the lack of validated trajectory biomarkers, unequal access to biologics and a gap between clinical innovation and the infrastructure needed to evaluate it. We outline research priorities focused on implementation and long-term outcomes.

Keywords: atopic dermatitis; disease modification; atopic march; biologic therapy; climatotherapy; implementation science.

1. Introduction

Atopic dermatitis (AD) affects about 103 million children worldwide [1]. In high-income countries, its 12-month prevalence among children aged 0-5 years reaches 16.2%, almost twice that seen in older age groups [2]. In one European cohort, direct and indirect family costs reached EUR 5,861 per year for a child with severe AD [3]. AD also disrupts the sleep, schooling and mental well-being of adolescents and their parents [4].

For decades, AD was treated as a reaction to flares. Emollients and topical anti-inflammatory agents came first, then non-specific immunosuppressants. Success meant rapid control of the current flare. The child's long-term course was rarely considered, even though early-onset AD has long been linked to later food allergy, asthma and allergic rhinitis. This sequence is known as the atopic march [5].

Targeted agents, now approved for children from 6 months of age, have changed the discussion. A growing question is whether early and deep suppression of inflammation can alter the natural course of the disease, with remission that persists after treatment is stopped and a lower risk of new atopic comorbidities [6, 7]. In April 2026, the International Eczema Council (IEC) proposed the first consensus definitions of low disease activity and remission [8]. In the same year, the American Academy of Dermatology issued its first pediatric guidelines. In them, systemic targeted therapy is no longer a last-resort option [9].

This review starts from the premise that redefining the goal of treatment is itself an innovation, as significant as any new molecule. It calls for new endpoints, measures of effectiveness and ways of organizing care. We address three questions. First, how convincing are the data on disease modification in children? Second, what place can traditional natural therapies, namely climatotherapy and balneotherapy, take within this new logic? Third, which methodological and organizational innovations are needed to turn what is technically possible into routine pediatric practice?

Literature was identified in PubMed and on the websites of journals and clinical trial registries. Priority was given to studies published in 2021-2026, to pediatric data and to randomized trials. Earlier publications were included when they remain key to their field, such as the first large emollient trials or the only controlled studies of climatotherapy. Only full-text peer-reviewed publications were included. Conference abstracts and reviews in journals without reliable indexing were not used. Adult data were used only where pediatric data are lacking, as

stated in the text. No formal risk-of-bias assessment or quantitative synthesis was performed. The terms "atopic dermatitis" and "atopic eczema" are used as synonyms throughout.

2. Heterogeneity and trajectories: the atopic march as a target

2.1. The march is one trajectory among many

The idea of a linear progression from eczema to food allergy and then to asthma and rhinitis arose from cross-sectional analyses of longitudinal cohorts. Latent class analyses of the same data show that about half of children with AD do not follow the march at all, even under its broad definition [5]. In a pooled analysis of British cohorts, the classic sequence was found in only 3.1% of children with atopic disease [10]. Several allergic diseases co-occur in the same child in 4-6% of the pediatric population, and they more often arise independently than one from another [11]. For this reason, the term atopic multimorbidity is increasingly used instead of the atopic march [10, 11].

In a clinical cohort of 894 children followed for 10 years, early transient AD accounted for 61%, early persistent AD for 15.2% and late-onset AD for 23.8%. Across all three phenotypes, signs of the march developed in 29.9% of the cohort. Sensitization to aeroallergens was associated both with persistence of dermatitis and with progression along the march [12]. Phenotypes describe the course of the dermatitis itself, whereas the march describes the onset of other allergic diseases, which can follow any phenotype. In a British cohort of 1.22 million mother-child pairs, maternal atopy increased the risk of AD in offspring, yet many children did not follow a sequential pattern [13].

These data matter for two reasons. First, much early AD resolves spontaneously. In Japanese cohorts, about 70% of children with dermatitis at 4 months reached complete remission by 18 months of age [14]. In the remaining children the dermatitis persists, and it is in this smaller group that the risk of progression is concentrated [12]. Second, the link between AD and food allergy is strong, with food allergy found in 32.7% of patients with AD [15]. Yet whether it is causal in an individual child is unclear, and the American Academy of Pediatrics considers the role of food allergy in the course of AD probably overestimated [16]. Early intervention should therefore be targeted rather than universal, aimed at a high-risk phenotype rather than at the diagnosis of AD as such. This phenotype includes early onset, severe and persistent disease and early sensitization.

2.2. The barrier as a gateway

The epidermal barrier is considered the pathogenic link between the skin and subsequent systemic sensitization. Filaggrin deficiency, altered ceramide composition of the stratum corneum, reduced synthesis of antimicrobial peptides and colonization by *Staphylococcus aureus* reinforce one another [17]. Food and inhaled allergens pass through the damaged barrier to antigen-presenting cells in the skin. Sensitization thus develops through the skin, before the first contact with the allergen through the gut [18]. Early skin dysbiosis in infants precedes the clinical onset of AD [19]. Whether this is a cause or a consequence of subclinical inflammation remains debated [17]. These processes are shown in Figure 1.

The relationship between barrier and inflammation runs both ways. IL-4 and IL-13 suppress filaggrin expression and the synthesis of long-chain ceramides in keratinocytes. Under inflammation, even an initially intact barrier therefore becomes permeable. A damaged barrier, in turn, lets allergens and microbial products in and sustains inflammation [17, 18]. This loop explains why acting on only one part of it, such as using emollients without anti-inflammatory treatment, gives a short-lived effect. It also suggests that deep early suppression of inflammation may create conditions for barrier repair, and it makes the barrier a shared target for pharmacological and non-pharmacological interventions.

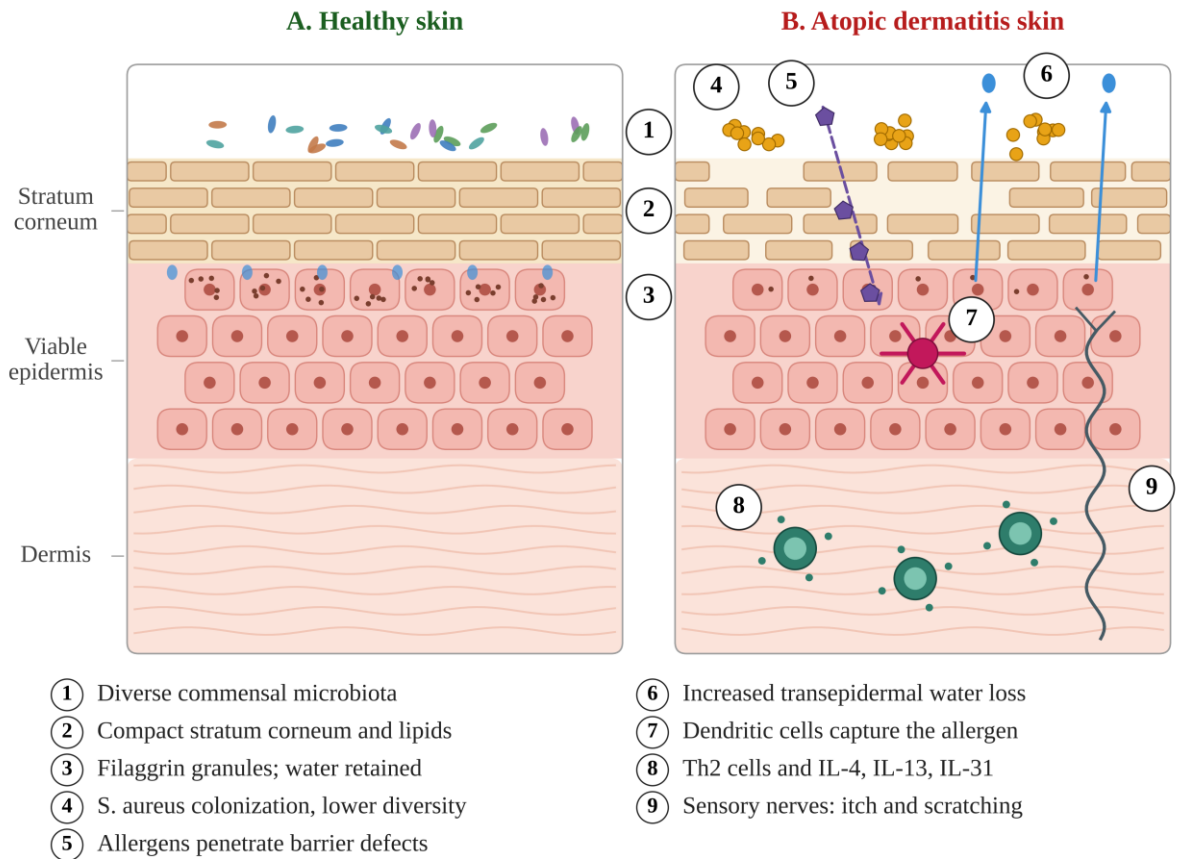

Figure 1. Structure of the epidermal barrier in healthy skin and in atopic dermatitis. Numbered markers are explained in the legend below the figure.

2.3. A window of opportunity and lessons from prevention trials

The first 2 years of life are seen as a period in which the skin and gut microbiota and the immune system calibrate one another. Disturbances during this period leave a lasting mark [20]. This led to the hypothesis that restoring the barrier from birth would prevent both AD and the march. Two large randomized trials tested it. In the British BEEP trial (n = 1394), daily emollient use during the first year did not reduce the incidence of AD in high-risk children [21]. The Norwegian-Swedish PreventADALL trial (n = 2397) also found no effect, and adherence to the intensive skin care regimen was low [22]. A 2022 Cochrane review concluded that skin care interventions in the first year of life probably do not prevent eczema, may increase the risk of food allergy and probably increase skin infections [23].

This negative result does not refute the barrier hypothesis, but it does refine it. Standard emollients applied to all at-risk children are too blunt a tool. The PEBBLES trial is testing a ceramide-dominant emollient with a physiological lipid ratio, and its results are expected in 2027 [24]. At the same time, skin biomarkers are emerging that could narrow the target group. Elevated TARC/CCL17 in skin tape strips at 2 months of age predicted the development of AD well before its clinical onset [25]. Combining early risk detection with targeted intervention, rather than universal prevention, now appears the most realistic way to change the disease trajectory. Until such targeted prevention is proven, early treatment of established disease, the domain of targeted therapy, remains the main lever.

3. Targeted therapy in children: from control to potential modification

3.1. A change of tools

Until recently, systemic treatment of severe AD in children relied on cyclosporine, methotrexate, azathioprine and short courses of systemic glucocorticoids. These agents act non-specifically, need laboratory monitoring and were not expected to change the course of the disease [26]. The 2026 pediatric guidelines of the American Academy of Dermatology give strong recommendations for dupilumab, tralokinumab, lebrikizumab, upadacitinib, abrocitinib and baricitinib, and an equally strong recommendation against systemic glucocorticoids [9].

Dupilumab, which blocks the IL-4Rα receptor, is approved for children from 6 months of age. In the LIBERTY AD PRESCHOOL trial of 162 children aged 6 months to 5 years, 28% of those on dupilumab reached clear or almost clear skin by week 16, compared with 4% on placebo. Skin infections were half as frequent [27]. For this review, it matters more that dupilumab also acts on the links between the skin and systemic sensitization. It gradually shifts the transcriptome of lesional skin towards a non-lesional profile and corrects epidermal abnormalities [28]. It lowers transepidermal water loss (TEWL) more than topical corticosteroids and cyclosporine do [29]. In children, it improves epithelial barrier function in both lesional and non-lesional skin [30]. In addition, it reduces *S. aureus* colonization and restores the diversity of the skin microbiota [31].

Targeted therapy thus acts not only on the immune component but also on the barrier and the microbiome, the same targets traditionally addressed by climatotherapy and balneotherapy [29-31]. Shared targets do not mean that the effects of the two approaches are compatible or additive; compatibility and additivity remain hypotheses. If they are combined, the question is one of sequence rather than competition. What needs to recover once inflammation is suppressed, and can non-pharmacological means speed this up?

3.2. Evidence on disease trajectory

No randomized data yet show that targeted therapy prevents the atopic march; the available evidence comes from observational studies and secondary analyses. A retrospective TriNetX cohort compared 2192 children who started dupilumab with the same number of propensity-matched children on conventional immunomodulators. The 3-year cumulative incidence of new asthma or allergic rhinitis was 20.1% versus 27.2% (hazard ratio 0.68; 95% CI 0.55-0.83). The reduction in asthma risk was significant only in preschool children [32]. Similar findings have so far appeared only in conference abstracts, which this review does not include.

A meta-analysis of 12 randomized trials showed that dupilumab reduced the rate of new or worsening allergic events by 34% compared with placebo [33]. However, the median age of participants was 35 years, follow-up did not exceed 52 weeks, and "allergic events" included itch and urticaria. Critics note that such an effect is hard to separate from better disease control alone [34]; only prospective studies can do so. They need prespecified trajectory endpoints (such as time to asthma onset), a comparator group in which inflammation is controlled to a similar degree and follow-up beyond 12 months.

The second line of evidence concerns remission after withdrawal. In an open-label extension study in children aged 6-11 years with severe AD, 29% of participants had maintained clear or almost clear skin for 12 weeks by week 52 and stopped treatment. Disease returned in 40% of them, after a mean of 13.5 weeks. The authors concluded that treatment probably needs to be continued to maintain the effect [35]. Preliminary data suggesting higher rates of treatment-free remission in preschool children have not yet been published as peer-reviewed full texts.

3.3. Other agents and the next wave

Tralokinumab, lebrikizumab and JAK inhibitors are highly effective in adolescents [36-38], but there are no data on their effect on disease trajectory in children. From the standpoint of modification, the most interesting agent is amlitelimab, an antibody against OX40 ligand. It does not deplete T cells; instead, it shifts the balance between effector and regulatory lymphocytes. In a phase 2b trial in adults, clinical response persisted for 28 weeks after the drug was stopped, even though its blood concentration had by then fallen below the threshold level [39, 40]. If phase 3 confirms this effect, the OX40 axis will become the first target for which durability of response off treatment is an explicit development goal.

Table 1 summarizes the key data, and the overall conclusion is cautious. Dupilumab remains the only candidate "modifier" with pediatric data [41]. Yet these data are retrospective and short, and they cannot separate a change in trajectory from effective control. A definitive answer requires prospective studies that start in infancy and include long follow-up after withdrawal [42].

Table 1. Targeted agents for pediatric atopic dermatitis: efficacy and data on durability of response and disease trajectory

Agent (target)	Age range of data	Key result	Data on trajectory or durability of response	Study design
Dupilumab (IL-4Rα)	≥ 6 months	IGA 0/1: 28% vs 4% at week 16 in children aged 6 months to 5 years [27]	Lower risk of new asthma or rhinitis: HR 0.68 [32]; treatment-free remission in some children, relapse in 40% of those who stopped [35]	RCT; retrospective cohorts; open-label extension
Tralokinumab (IL-13)	12-17 years	EASI-75: 28.6% and 27.8% vs 6.4% [36]	No pediatric data	RCT

Lebrikizumab (IL-13)	12-17 years	IGA 0/1 in 62.6% at week 52 [37]	No pediatric data	Open-label study
Upadacitinib (JAK1)	12-17 years	EASI-75 in 84-89% at week 76, no new safety signals [38]	No pediatric data	RCT with extension
Amlitelimab (OX40L)	Adults; phase 3 ongoing	Significant EASI reduction vs placebo [39]	Response maintained 28 weeks after withdrawal [39, 40]	Phase 2b RCT

4. What counts as modification and remission

Even if targeted therapy does change the course of AD, this cannot yet be proven, because for a long time there was no agreement on what remission means. Early attempts at standardization relied on a treat-to-target strategy. A 2021 international consensus set treatment goals at months 3 and 6 of systemic therapy in adults [43]. It was later supplemented with an updated algorithm and criteria for minimal disease activity [44]. These documents answered the question "Is treatment working well enough?" but not "Has the disease changed?"

The 2026 IEC consensus was the first to separate control on treatment from remission without it [8]. The definitions combine objective signs with itch (Figure 2). Low disease activity corresponds to vIGA-AD 2 or EASI ≤ 7 with PP-NRS ≤ 4. Very low disease activity corresponds to vIGA-AD 0/1 or EASI ≤ 3 with PP-NRS 0/1. Complete control on treatment requires vIGA-AD 0 or EASI 0 with PP-NRS 0/1 for at least 6 months. Treatment-free remission requires the same values for at least 12 months after therapy is stopped. The definitions, agreed by 103 experts in a Delphi process, rest on expert opinion and have not been prospectively validated [8].

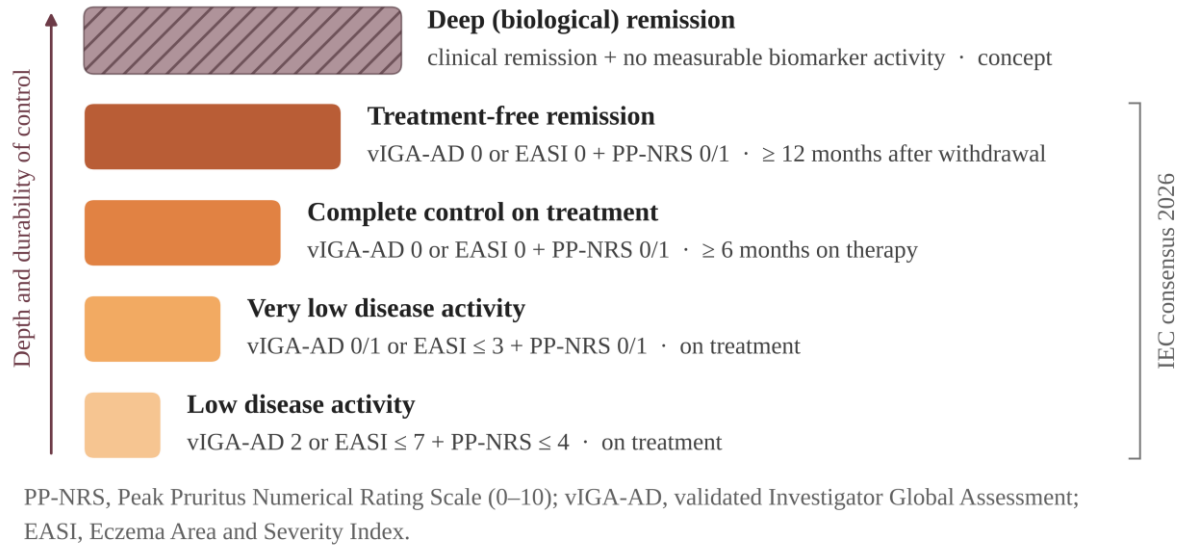

Figure 2. Levels of control and remission in atopic dermatitis according to the 2026 International Eczema Council consensus, with an added level of biological remission.

Comparison with pediatric data shows how wide the gap is. In open-label extension studies of dupilumab, "remission" meant vIGA 0/1 for 12 weeks on treatment, and persistence of the effect after withdrawal was assessed over a few months [35]. By the standards of the new consensus, none of these results yet qualifies as treatment-free remission. Proposed extended frameworks add intermediate states. One introduces "taper-responsive control", defined as response maintained for at least 3 months after the dose is cut by 50% or more [45]. Another introduces a disease activity index in which deep remission combines clinical remission with no measurable biological activity [46].

This last requirement is essential, because clear skin is not the same as healthy skin. Transcriptomic analysis has shown that AD carries a stable core signature that persists even in non-lesional skin. Even after successful treatment, the skin profile remains markedly different from normal [47]. Dupilumab shifts it substantially, but not to full normalization [28]. For assessing biological activity in children, TARC/CCL17 and IL-13 are the best studied; their serum levels correlate with SCORAD. A panel of 18 analytes measured at enrollment predicted changes in severity 4 years later [48]. Periostin, total IgE, eosinophils and non-invasive methods based on skin

tape strips complement this set. None of these markers has yet been validated as a predictor of disease trajectory [49].

In children, the task is complicated by two further factors. An infant cannot rate itch on a numerical scale, so the symptom component of the definitions has to be replaced with a parent-reported measure. In addition, much early AD resolves spontaneously [14]. Without a control group, remission after drug withdrawal cannot be distinguished from the natural course of the disease.

A pediatric definition of disease modification will therefore probably need to be composite. As a working framework that requires validation, we propose four domains, each already discussed in the literature. The clinical domain (vIGA-AD or EASI) follows the IEC consensus, and the symptom domain adapts its itch criterion to parent report, adding sleep [8]. The functional domain (TEWL) draws on barrier studies [29]. The biological domain (TARC/CCL17 or a multi-marker panel) builds on pediatric biomarker work [48, 49]. Composite frameworks combining such elements have also been proposed [45, 46]. Each domain can already be measured on its own. Validating the framework will require prospective pediatric cohorts and registries that record all four domains in parallel (Section 7). What is missing now is an agreed threshold for each in children of different ages. Also missing are data on which combination of thresholds predicts durable remission.

This is a gap typical of innovation, between what is technically possible and the infrastructure needed to evaluate it. Drugs that may influence the disease trajectory are already used in infants. The criteria for capturing that influence have only just been formulated, and only for adults. Registries with a common dataset exist, but their pediatric follow-up is still short [50, 51]. Defining disease modification as treatment-free remission combined with prevention of comorbidities [7] provides a framework, but not a tool for measuring it.

5. Adjunctive natural therapies: from tradition to evidence-based integration

Next to targeted therapy, climatotherapy and balneotherapy are easily dismissed as outdated or "alternative" methods. European guidelines discuss them among non-pharmacological and complementary interventions [52]. Most systematic reviews report a moderate benefit supported by low-quality evidence [53, 54]. What may be new is not the methods themselves but building them into modern protocols, with a standardized description of the intervention, measurable endpoints and patient selection criteria. What matters here is less the size of the effect than which mechanisms it acts on and how long it lasts. Key pediatric studies are summarized in Table 2.

5.1. Climatotherapy

The strongest pediatric data concern climatotherapy. In a Norwegian randomized trial, children aged 4-13 years with moderate to severe AD spent 4 weeks in Gran Canaria. Their SCORAD fell from 37.2 to 12.2, *S. aureus* colonization decreased, and at 3 months SCORAD was still lower than in children who had stayed at home (21.2 vs 30.6) [55]. In 72 Czech children of preschool and school age treated for 4 weeks at the Dead Sea, SCORAD improved by 87.5% by the end of the course, a change of similar magnitude to that in a non-randomized comparison group on topical corticosteroids (86.1%). Both groups kept low scores over 18 months of follow-up. However, the groups were not randomized, and only 65.3% of the climatotherapy group remained at the end of follow-up [56].

The only randomized trial with long follow-up gave a more modest result. In the DAVOS trial, 88 children aged 8-18 years with difficult-to-treat AD received a 6-week multidisciplinary program either in an Alpine clinic or as outpatients in the Netherlands. The Alpine group did better at 6 weeks in disease activity and quality of life, but long-term outcomes were similar in both arms [57]. This suggests that much of the effect comes from the structured program of care and education, not from the climate alone.

5.2. Balneotherapy and marine salts

The evidence on balneotherapy is even more heterogeneous. In a 2023 systematic review, only 22 of 424 publications met the inclusion criteria [53]. In a 2024 review of thermal mineral water baths, only one of the eight included studies concerned AD [54]. The largest pediatric series included 867 children (mean age 5.9 years) treated at the Comano thermal spring in Italy. AD severity fell significantly after the course, and some subgroups responded better than others [58]. However, there was no control group and no follow-up after the course. Thermal water balneotherapy has also been linked to changes in the gut microbiota [59]. The included studies used very different waters, from thermal spring water to marine salts [53, 54]. Because water composition differs, balneotherapy is better described as a family of interventions with distinct properties than as a single exposure.

The proposed mechanisms of natural therapies include the osmotic and anti-inflammatory effects of minerals, restored hydration of the stratum corneum, moderate ultraviolet exposure, reduced *S. aureus* colonization, and less itch and stress [53, 55]. For narrowband ultraviolet B, the therapeutic counterpart of sun exposure, a Cochrane review of 32 studies (1219 participants) concluded that, compared with placebo, it may reduce AD severity and itch, although the certainty of evidence is low [60].

This is not enough to make future studies comparable. Balneotherapy publications rarely report the mineral composition and temperature of the water, the duration and frequency of sessions, concomitant treatment or sun exposure. Without this information, results can neither be pooled in a meta-analysis nor reproduced at another center [53, 54]. A standardized description of the intervention is the first requirement for bringing natural therapies into evidence-based medicine.

5.3. Herbal medicine

Herbal medicine remains the most contested area. A 2025 systematic review included 51 RCTs with 3763 participants. Some topical preparations, St John's wort and a combination of aloe vera with olive oil, showed signs of efficacy. A meta-analysis of 13 RCTs of evening primrose oil found no benefit over placebo [61]. This agrees with a Cochrane review of 27 studies of evening primrose and borage oils [62]. Herbal medicine is best left out of the integrative model until standardized preparations of reproducible composition are tested in blinded pediatric RCTs with adequate follow-up.

5.4. Implications for the model

Natural therapies act on different axes of pathogenesis than targeted therapy does. Their targets are the barrier, the microbiome, sleep, psychological burden and skin care skills, not the cytokine cascade. They are thus potential tools for the residual burden that persists despite good control of inflammation, not competitors to biologics. Yet none has been studied alongside targeted therapy, and almost all studies predate biologics. The only pediatric RCT with long follow-up found no lasting advantage of climate as such [57].

Table 2. Evidence base for adjunctive natural therapies in pediatric atopic dermatitis. The level of evidence is a qualitative assessment by the authors, not a formal GRADE rating

Therapy	Design and sample	Main result	Follow-up after the course	Main limitations	Level of evidence
Subtropical climatotherapy (Gran Canaria) [55]	RCT, children aged 4-13 years	SCORAD 37.2 → 12.2; less *S. aureus*	3 months, effect partly maintained	Small sample, no blinding	Low
Dead Sea climatotherapy [56]	Prospective observational study, 72 children; non-randomized comparison with 44 children on topical corticosteroids	SCORAD improvement of 87.5% (vs 86.1% with corticosteroids)	18 months; low scores maintained in both groups	No randomization; 35% lost to follow-up	Very low
Alpine climate, DAVOS program [57]	Pragmatic RCT, 88 children aged 8-18 years	Advantage at 6 weeks	6 months; no lasting advantage	No blinding; contribution of the care program	Low to moderate
Thermal water balneotherapy [58, 59]	Observational series, 867 children; reviews	Significant reduction in severity immediately after the course	Not assessed	No control group; water composition varies	Very low
Narrowband UVB [60]	Cochrane review, 32 studies, 1219 participants	May reduce severity and itch vs placebo (low certainty)	Few data	Few children; long-term safety concerns	Low
Herbal medicine [61, 62]	Systematic reviews, 51 and 27 RCTs	Evening primrose oil no better than placebo; some topical preparations promising	No data	Non-standardized preparations, high risk of bias	Low

6. An integrative model: the hybrid protocol hypothesis

Two observations follow from the preceding sections. Targeted therapy suppresses inflammation quickly and deeply, and partly restores the barrier and the microbiome along the way [29-31]. Yet after it is stopped, the disease returns in a substantial share of children [35]. Natural therapies act on the barrier, the microbiome and behavior, but without suppression of inflammation their effect does not last [55, 57]. From this we derive a hypothesis, presented as a conceptual model rather than a clinical recommendation. Targeted therapy "opens a window" in which inflammation is suppressed. A structured adjunctive program uses this window to consolidate barrier function and skin care skills. This should increase the chance of maintaining remission during de-escalation (Figure 3).

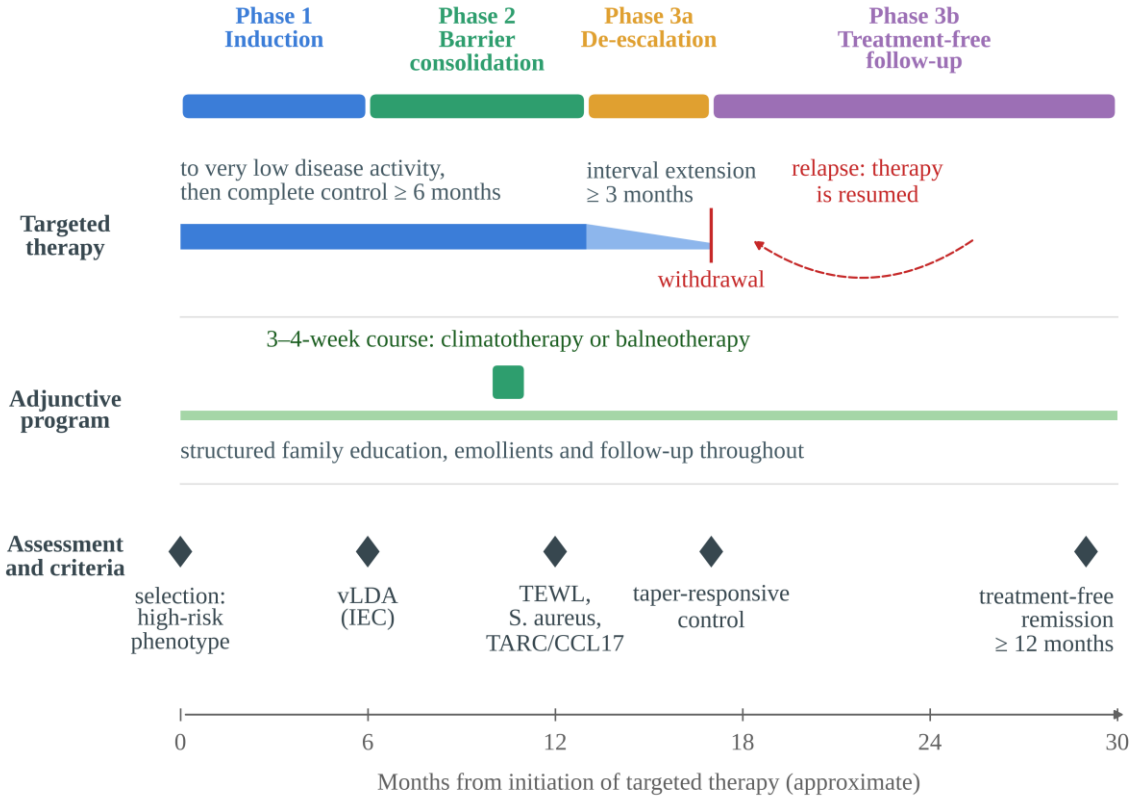

Figure 3. Conceptual model of the hybrid protocol: induction of control, barrier consolidation, and de-escalation with long-term follow-up.

The model has three phases.

1. Induction. A child with a high-risk phenotype starts targeted therapy in line with current guidelines. The aim is very low disease activity by IEC criteria [8]. In parallel, the family receives structured education, which reduces AD severity in pediatric RCTs [63].
2. Consolidation. After at least 6 months of complete control, the child completes a 3-4-week course of climatotherapy or balneotherapy. The course is embedded in a program of skin care, education and psychological support. This format, rather than climate alone, has the best supporting evidence [57]. Besides clinical scores, this phase assesses TEWL, *S. aureus* colonization and serum TARC [48] as candidate biomarkers of readiness for de-escalation.
3. De-escalation and follow-up. The dosing interval is gradually extended, guided by taper-responsive control for at least 3 months [45], and therapy is then stopped. Follow-up continues for at least 12 months so that the result can qualify as treatment-free remission [8]. If relapse occurs, therapy is resumed without repeating the whole protocol.

Testing the model requires a prespecified set of outcomes. The natural primary endpoint is treatment-free remission for at least 12 months by consensus criteria [8]. Such an endpoint requires long-term funding and participant retention. In pilot studies, it can reasonably be replaced by an intermediate endpoint, time to relapse after withdrawal. Secondary outcomes may include the incidence of new atopic comorbidities, namely asthma, allergic rhinitis and food allergy [32]. They may also include changes in TEWL [29], *S. aureus* colonization [31]

and the quality of life of the child and family [3, 4]. Such a set would allow the model to be evaluated both as a clinical intervention and as an organizational innovation.

Putting the model into practice raises organizational as well as clinical questions. Who refers the child and manages transitions between phases: the dermatologist, the allergist, the pediatrician or the spa physician? In a multidisciplinary program for children with difficult-to-control AD, joint visits by a dermatologist, an allergist and a clinical pharmacist, with standardized assessment and shared education modules, produced a measurable reduction in disease severity [64]. Separating the effect of an adjunct from that of ongoing targeted therapy calls for a factorial design with randomization at consolidation. Finally, who needs the model most? Children with predominant barrier dysfunction and *S. aureus* colonization, whose TEWL remains high after induction, may plausibly benefit most. This hypothesis has not been tested.

Adherence remains a serious obstacle. In pediatric studies it is low even for simple topical regimens [65]. Education programs are directed mostly at caregivers [66]. A three-phase protocol lasting 2 years or more (Figure 3) will need tools for retaining families, from digital follow-up to a care coordinator. Without them, the model will remain theoretical.

The model also carries a risk of widening inequity. A course of climatotherapy or balneotherapy requires the family to travel and to pay. Without compensating mechanisms, such as regional programs, subsidies and remote follow-up during induction and de-escalation, the protocol would be available only to well-off families (see Section 7). The DAVOS trial offers a partial answer: its outpatient arm, treated in the home country, had long-term outcomes similar to those of the Alpine arm [57]. A structured program delivered locally could therefore be the default consolidation option, with climatotherapy reserved for selected cases. Funding of the consolidation phase (public reimbursement, insurance or a mixed model) depends on the health system and lies beyond this review, but it should be settled when the model is designed.

7. Barriers to implementation and research priorities

The path from the concept of disease modification to routine pediatric practice runs through several barriers. We group them into five domains at different levels of analysis: methodological (how to measure), evidence (what is known), organizational (who provides care and how), economic (who pays and who has access) and ethical (which values count). The domains are linked: the methodological gap limits the evidence base, which in turn constrains organizational and economic decisions. A summary is given in Table 3.

Methodological barrier. There are no validated trajectory biomarkers and no pediatric definitions of remission (Section 4). Without them, children cannot be selected for early intervention, and its long-term effect cannot be captured.

Evidence barrier. Almost all data on natural therapies predate targeted therapy, and randomized trials with follow-up beyond 6 months are practically absent [53, 54, 57]. Targeted therapy, by contrast, has short RCTs and retrospective cohorts but no prospective studies of disease trajectory.

Organizational barrier. Even well-established guidelines are followed unevenly. In a survey of Dutch general practitioners, adherence to key recommendations of the national guideline ranged from 43.7% to 98.1%, and it was lowest for topical corticosteroids; non-adherence was linked mainly to physicians' knowledge gaps and attitudes [67]. A hybrid protocol involving several specialties and spa services will be harder still to implement. It will need a coordinator, shared care pathways and a common dataset.

Economic barrier and unequal access. Annual family costs rise with AD severity [3], and data on the economic burden of pediatric AD as a whole are scarce [68]. Full-text cost-effectiveness evaluations of targeted therapy in children are practically non-existent. Inequity is an even more pressing problem. In a cohort of 12,918 children in Florida, Black children were less likely to receive dupilumab (OR 0.43), and the same was true of Hispanic children [69]. Similar disparities in access to advanced systemic therapy were found in a multicenter sample of 1928 patients, including 577 children [70]. Climatotherapy, which requires weeks of travel, may widen this gap further.

Ethical barrier. The long-term safety of targeted therapy started in infancy is still being studied in registries [50, 51]. Research in children requires parental consent and, from a certain age, the child's own assent. The burden on families, including missed work and chronic sleep loss in parents [71], must be considered when multi-year protocols are planned.

This leads to five research priorities:

1. adaptation and prospective validation of the remission definitions [8] in children, including parent-reported itch;
2. randomized trials of adjunctive programs alongside targeted therapy, using factorial designs and follow-up of at least 12 months after withdrawal;
3. studies of how climatic and environmental factors relate to long-term outcomes of AD;
4. international registries with a common dataset to assess disease trajectory and safety [50];

5. economic evaluation of integrative models that accounts for family costs and equity of access.

7.1. Limitations of this review

This narrative review does not claim the completeness of a systematic search. Data on targeted therapy come mainly from high-income countries, and some of the mechanistic studies were conducted in adults and adolescents [28, 29]. Conference abstracts were deliberately excluded. This may have led us to underestimate recent pediatric data on remission after withdrawal, but it avoided reliance on results that have not been peer reviewed. Studies of natural therapies are often conducted at the spas themselves or with support from thermal water manufacturers [58, 59], which increases the risk of bias. Finally, the integrative model is a hypothesis derived from the evidence, not a tested intervention.

Table 3. Barriers to implementing the integrative model and research priorities

Domain	Main barrier	What is known	Research priority
Methodology	No pediatric definitions of remission or trajectory biomarkers	2026 IEC consensus, developed for adults [8]; TARC and IL-13 correlate with severity [48]	Validation of definitions in children; biomarker panels
Evidence base	No RCTs of natural therapies alongside targeted therapy	One pediatric RCT with long follow-up, no lasting effect [57]	Factorial RCTs with ≥ 12 months of follow-up after withdrawal
Organization of care	Fragmented care; uneven adherence to guidelines	Adherence 43.7-98.1% [67]; benefit of multidisciplinary clinics [64]	Coordination models, shared care pathways
Economics and access	High cost of biologics; unequal access	OR 0.43 for Black children [69]; inequity in a multicenter sample [70]	Evaluation of costs and equity of access
Ethics and safety	Long-term safety in infants; burden on families	Registries with short pediatric follow-up [50, 51]; parental burden [71]	Multi-year registries; family support tools

8. Conclusions

Pediatric atopic dermatitis is no longer viewed as a disease of symptoms; it is increasingly seen as a disease with a trajectory. Longitudinal cohorts show that only a minority of children follow the classic march, so intervention should be directed at the high-risk phenotype. Targeted therapy has driven this change in approach. In children, dupilumab is associated with a lower risk of new atopic comorbidities and, in some cases, with remission after withdrawal. These data, however, are still observational and short-term. The first consensus definitions of remission appeared only in 2026 and have not yet been adapted for children.

Disease modification is not only a matter of new molecules. Natural therapies, namely climatotherapy and balneotherapy, act on the barrier, the microbiome and family behavior. These are the axes of disease that targeted therapy does not fully address. Their evidence base is dated and needs updating in the era of biologics.

The proposed hybrid model of induction, consolidation and de-escalation remains a hypothesis, but it poses testable questions. Implementing it will require changes in evaluation methods, care organization and equity of access. The most promising research lies at the interface of pharmacology, climatology and health services research. A necessary first step is agreement on pediatric definitions of remission, for example by extending the IEC consensus process to children [8], and an international registry built on a common core dataset such as that of the TREAT taskforce [50]. Without these, neither targeted therapy nor adjunctive therapies can be shown to modify the course of the disease.

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