Atopic Dermatitis: State of the Art and Emerging Treatments

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Disclosures

› Investigator, Regeneron, Incyte
› Advisory Boards, Regeneron, Sanofi-Genzyme, Abbvie, Dermira, Leo, Lilly, Pfizer
Global variations in prevalence of eczema symptoms in children from ISAAC Phase

The most common chronic skin disease seen in both developed and developing countries
- Significant impact on QoL of patients and caregivers
- Often associated with both atopic & nonatopic comorbidities
- Not “outgrown” in a significant number of patients

Atopic dermatitis: a disease of altered skin barrier and immune dysregulation

Non-lesional

RDGP: residual disease genomic profile

Normal appearing (non-lesional) skin in AD patients is NOT normal!

Therapeutic targets
Immune cell subsets mediating strong, chronic local inflammation that potentially spreads beyond the skin, mediating systemic inflammation

Potential trajectories of disease progression toward asthma and AR in patients with AD initially (the atopic march)

The Atopic March... Fact or folklore?

Recent insights into atopic dermatitis and implications for management of infectious complications

Increased susceptibility to infection or colonization with microbial organisms: S. aureus*, Herpes simplex

*epidemic of CA-MRSA in US

Microbiome in AD

Skin commensals and intact skin barrier promote tolerance induction, while skin barrier impairment and dysbiosis can drive type 2 inflammation.

Transplantation of antimicrobial CoNS reduces survival of S. aureus on human skin

Atopic dermatitis subjects colonized with S. aureus have a distinct phenotype and endotype

- Compared to S. aureus (-) AD pts, S. aureus (+) AD pts had more severe disease based on all scoring systems except itch (NRS)
  - higher levels of type 2 biomarkers (eosinophil count, tlgE, CCL17, and periostin)
  - significantly greater allergen sensitization (Phadiatop and tlgE)
  - greater barrier dysfunction (TEWL and SC integrity) and higher serum LDH
- *FLG* mutations did not associate with S. aureus (+) colonization
- Adult AD pts colonized with S. aureus have more severe disease, greater type 2 immune deviation, allergen sensitization, barrier disruption, and LDH elevation than noncolonized AD subjects

Altered composition of epidermal lipids correlates with Staphylococcus aureus colonization status in atopic dermatitis

Lipid abnormalities in atopic skin are driven by type 2 cytokines

- Lipids in the stratum corneum of AD patients differ substantially in composition from healthy subjects.
- RNA sequencing analysis performed on stratum corneum of AD as compared with healthy subjects identified decreased expression of fatty acid elongases ELOVL3 and ELOVL6 that contributed to observed changes in atopic skin lipids.
- IL-4/IL-13 inhibited ELOVL3 and ELOVL6 expression in keratinocyte cultures in a STAT6-dependent manner.
- Data strongly support the pathogenic role of type 2 immune activation in AD skin lipid metabolism.

Berdyshev E, et al. JCI Insight 2018;3:e98006
Minimally invasive skin tape strip RNA sequencing identifies novel characteristics of the type 2–high atopic dermatitis disease endotype

Immune activation signature in AD subjects reflects significant upregulation of type 2 inflammatory genes and presence of activated T helper 2 and dendritic cells

The nonlesional skin surface distinguishes atopic dermatitis with food allergy as a unique endotype

Leung DY, et al. Sci Transl Med 2019;11
Duodenal mast cells are increased in patients with AD

• Independent of overt food allergy & not simply result of elevated serum IgE
• Results show a skin-to-gut crosstalk in which mechanical skin injury promotes food anaphylaxis by driving intestinal MC expansion, in addition to facilitating sensitization to food allergens

Skin-to-gut cross-talk…

- Mechanical skin injury promotes intestinal mast cell expansion
- Intestinal mast cell expansion requires skin-derived IL-33 and gut-derived IL-25
- Intestinal mast cell expansion requires ILC2 activation by IL-33 and IL-25
- ILC2-derived IL-4 and IL-13 directly cause intestinal mast-cell expansion

Atopic Dermatitis Yardstick

Special Article

Atopic dermatitis yardstick: Practical recommendations for an evolving therapeutic landscape

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Abstract

The implementation of treatment guidelines for atopic dermatitis is challenging, in part because of different guidance documents being used by different groups of specialists and in part because the language of guidelines often reflects the evidence base rather than the practical "how to." The Atopic Dermatitis Yardstick is part of a series developed in response to the need to proactively address the loss of disease control for atopic dermatitis at all levels of severity. It presents a comprehensive update on how to conduct a sustained step-up in therapy for the patient with inadequately controlled or poorly controlled atopic dermatitis. Patient profiles, based on current guidelines and the authors' combined clinical expertise, provide a practical and clinically meaningful guide to aid physicians in helping their patients achieve the goal of clear to almost clear. The intent is not to replace guidelines but to complement these recommendations incorporating the latest research and therapies.

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Introduction

Atopic dermatitis (AD) is a chronic, relapsing inflammatory skin disease—one of the most common inflammatory skin diseases worldwide, with an estimated prevalence of up to 25% of children and 7% of adults in the United States. AD typically occurs in infancy and early childhood, with an onset in the first year of life reported for 60% to 85% of children and by 5 years of age for at least 85%. However, AD can present at any age, and although most childhood-onset symptoms resolve before adulthood, persistent (albeit often in milder form) is relatively common. Up to 50% of adult patients are first diagnosed in adulthood, and 30% of childhood cases persist into the adult years. Managing AD at any age can be challenging.

Atopic dermatitis is a diagnosis based on clinical presentation. Current research detailing the underlying mechanisms of AD (Fig 1; eCommentary 1) holds hope that biomarkers will be available to confirm the diagnosis and possibly differentiate various AD phenotypes (eg, intrinsic vs extrinsic AD, pediatric AD, Asian-origin AD). However, the current reality is that AD is diagnosed by symptoms and exclusion (Table 1).

The clinical presentation of AD is characterized by (1) pruritus, (2) recurrent lesions (associated with T helper cell type 2 (Th2) and Th22 inflammation), and (3) dry skin (related to epidermal barrier...
Atopic Dermatitis Yardstick

- Indicated for patients with mild-to-moderate AD, ages 2 years and older.
- Indicated for patients with moderate-to-severe AD, ages 18 years and older.
- Not FDA-approved to treat AD; FDA approved to treat AD, but not recommended for long-term maintenance.


1. Indicated for patients with mild-to-moderate AD, ages 2 years and older.
2. Indicated for patients with moderate-to-severe AD, ages 18 years and older.
3. Not FDA-approved to treat AD.
4. FDA approved to treat AD, but not recommended for long-term maintenance.
Atopic Dermatitis Yardstick flow diagram

Editorial

Targeted therapy for allergic diseases: At the intersection of cutting-edge science and clinical practice

Mark Boguniewicz, MD, and Donald Y. M. Leung, MD, PhD  Denver, Colo
ClinicalTrials.gov – January 10, 2020

› Atopic dermatitis 880 studies registered!
› Brief review of (primarily) published studies with biologics & small molecules
Developing specific targets

- Microbial directed therapies
- Pruritus directed therapies
- Immunologic therapies
- Barrier directed therapies

J Allergy Clin Immunol 2014;134:769
AD phenotypes and related endotypes

A Study of Crisaborole Ointment 2% in Children Aged 3-24 Months With Mild to Moderate Atopic Dermatitis

› 4-week study to evaluate safety, pharmacokinetics and efficacy of crisaborole ointment 2% applied BID in subjects 3 months to less than 24 months of age with mild-to-moderate AD

› Study completed, results pending

ClinicalTrials.gov 01/2020
Recombinant Gamma Interferon in Treatment of Patients with Atopic Dermatitis and Elevated IgE Levels

MARK BORGULIECK, M.D., Boston, Massachusetts; RICHARD S. JAFFE, M.D., AYUD GUPTA, M.S., San Francisco, California; and DAVID S. ORTIZ, B.S., BAYLOR COLLEGE, ROSA S. SCHNITZER, M.D., and RICHARD B. BROWN, M.D., Washington, D.C.

Abstract

The mechanisms involved in the initiation and maintenance of skin inflammation in atopic dermatitis (AD) are poorly understood. Recent data suggest that the pattern of cytokines expressed locally plays a critical role in modulating the nature of tissue inflammation. In this study, we used in situ hybridization to investigate the expression of interleukins (IL-1, IL-2, IL-4, IL-5, and interferon-gamma (IFN-γ) messenger RNA (mRNA) in skin biopsies from acute and chronic skin lesions of patients with AD. As compared with normal control skin or uninvolved skin of patients with AD, acute and chronic skin lesions had significantly greater numbers of cells that were positive for mRNA, IL-4 (p < 0.01), and IL-5 (p < 0.01), but not for IFN-γ mRNA expressing cells. However, as compared with acute AD skin lesions, chronic AD skin lesions had significantly fewer IL-4 mRNA-expressing cells (p < 0.01), but significantly greater IL-5 mRNA (p < 0.01). T cells constituted the majority of IL-5-expressing cells in acute and chronic AD lesions. Chronic lesions also expressed significantly greater numbers of activated CD3+ cells than acute lesions (p < 0.01). These data indicate that although acute and chronic AD lesions are associated with increased activation of IL-4 and IL-5 expression, initiation of acute skin inflammation in AD is associated with a predominance of IL-4 expression whereas maintenance of chronic inflammation is predominantly associated with increased IL-5 expression and eosinophil infiltration. (J Clin Invest. 1994. 94:876–876.) Key words: atopic dermatitis • inflammation • cytokines • eosinophils • T cells

Introduction

Atopic dermatitis (AD) is a chronic skin disease affecting up to 10% of children and is the major cause of occupational-related disability caused by skin disease. It is associated with intense pruritus, increased serum IgE levels, and peripheral blood eosinophils (1, 2). The actual events that result in this inflammatory skin condition are poorly understood. However, it is thought that genetic susceptibility, environmental triggers such as allergens, and altered immune responses contribute to its pathogenesis (3). Acute and chronic skin lesions in AD are characterized by the infiltration of activated T cells and mononuclear phagocytes (4, 5). Although eosinophils are not prevalent by routine histology, chronic AD is associated with extensive dermal deposition of eosinophil granule major basic protein (6). In this regard, serum levels of IL-2 and eosinophil cationic protein have been reported to correlate with severity of skin disease (7, 8). Favorable clinical responses of AD patients to cyclosporin A also implicate immune activation as an important mechanism in the pathogenesis of AD (9, 10).

Identification of the immunoregulatory elements that play a role in maintaining and mediating skin inflammation in AD is critical for the development of new approaches to treat this common and often disturbing skin disease. Studies of T cell clones support the concept that activation of a subset of helper cells leads to the release of cytokines important in the pathogenesis of allergic disease. In the skin, two types of CD4+ T helper cell clones have been described on the basis of their cytokine gene transcription and secretion (11). TH1 type (Th1) cells express mRNA and secrete IL-2 and interferon-gamma (IFN-γ) but not IL-4 or IL-5. In contrast, Th2 cells elaborate IL-4 and IL-5 but not IFN-γ. Both populations of T cell clones produce IL-3, GM-CSF, and TNF-α. IL-4 acts on some IgE-positive-specific mast cells involved in immune responses to allergens (12), promotes mast cell growth (13), and induces the expression of vascular cell adhesion molecule-1 (VCAM-1), an adhesive molecule involved in the migration of mononuclear cells and eosinophils into sites of tissue inflammation (14). IL-5 promotes the differentiation, vascular endothelial adhesion and survival of eosinophils as well as enhances histamine release from basophils (reviewed in
Dupilumab, a fully human monoclonal antibody targeting IL-4 receptor-alpha

Hamilton JD, et al. Immunotherapy 2015;7:1043
**Dupilumab approved in the US**
- Pts aged ≥ 12 years with moderate-to-severe AD uncontrolled by topical prescription medicines or when those medications are not advised
- As add-on maintenance treatment in pts with moderate-to-severe asthma aged ≥ 12 years with an eosinophilic phenotype or with oral steroid dependent asthma
- As add-on maintenance treatment in adult patients with inadequately controlled chronic rhinosinusitis with nasal polyposis

**In Europe**
- Adult pts with moderate-to-severe AD who are candidates for systemic therapy & also indicated in adults and adolescents 12 years and older as add-on maintenance treatment for severe asthma with type 2 inflammation characterised by raised blood eosinophils and/or raised FeNO, who are inadequately controlled with high dose ICS plus another medicinal product for maintenance treatment

**In Japan**
- Pts whose AD is uncontrolled with existing therapies

**In Australia**
- Adult patients with moderate to severe atopic dermatitis & maintenance treatment of moderate-to-severe asthma in patients 12 year and older whose asthma is not controlled with their current asthma medicines
Dupilumab progressively improves systemic and cutaneous abnormalities in patients with atopic dermatitis

AD pts from phase 2 & 3 trials pre-/post-dupilumab

› Patient photos

Dupilumab provides important clinical benefits to patients with atopic dermatitis who do not achieve clear or almost clear skin according to the Investigator’s Global Assessment: a pooled analysis of data from two phase III trials

Among patients with IGA > 1 at wk 16, dupilumab significantly improved several outcome measures compared with placebo:
- EASI (-48.9% vs. -11.3%, P < 0.001)
- pruritus NRS (-35.2% vs. -9.1%, P < 0.001)
- affected BSA (-23.1% vs. -4.5%, P < 0.001)
- POEM score ≥ 4-point improvement (57.4% vs. 21.0%, P < 0.001)
- DLQI score ≥ 4-point improvement (59.3% vs. 24.4%, P < 0.001)

IL-4Rα blockade by dupilumab decreases Staphylococcus aureus colonization and increases microbial diversity in atopic dermatitis

- Bacterial DNA analyzed from swabs from lesional (L) and nonlesional (NL) skin in DBPC study of 54 pts with moderate-to-severe AD randomized 1:1 and treated with dupilumab 200 mg wkly or placebo for 16 wks.
- Microbial diversity and relative abundance of *Staph* assessed by DNA sequencing of 16S rRNA and absolute *S. aureus* abundance measured by quantitative PCR.
- Before treatment, L skin had lower microbial diversity and higher overall abundance of *S. aureus* than NL skin.
- During dupilumab treatment, microbial diversity increased and abundance of *S. aureus* decreased and correlated with clinical improvement and biomarkers of type 2 immunity.

Infections in dupilumab clinical trials in atopic dermatitis: A comprehensive pooled analysis

- 2932 pts, 1091 received placebo, 1095 dupilumab 300 mg wkly and 746 dupilumab 300 mg q 2 wks
- Treatment groups had similar infection rates overall per 100 pt-yrs (placebo, 155; dupilumab wkly, 150; dupilumab q 2 wks, 156; dupilumab combined, 152) and similar non-skin infection rates
- Serious/severe infections reduced with dupilumab (RR 0.43; p < 0.05), as were bacterial and other non-herpetic skin infections (RR 0.44; p < 0.001)
- Herpesviral infection rates overall were slightly higher with dupilumab than placebo, clinically important herpesviral infections (EH, zoster) less common with dupilumab (RR 0.31; p < 0.01)
- Systemic anti-infective medication use lower with dupilumab

Conjunctivitis in dupilumab clinical trials

› Evaluation of randomized placebo-controlled trials of dupilumab in AD (n = 2629), asthma (n = 2876), CRSwNP (n = 60) and EoE (n = 47)
› Conjunctivitis more frequent with dupilumab treatment in most AD trials
› In dupilumab trials in other type 2 diseases, incidence of conjunctivitis overall very low and similar for dupilumab and placebo
› In AD, incidence of conjunctivitis associated with AD severity and prior history of conjunctivitis
› Etiology and treatment of conjunctivitis in dupilumab-treated patients require further study

Dupilumab shows long-term safety and efficacy in moderate-to-severe atopic dermatitis patients enrolled in a phase 3 open-label extension study

› Ongoing, multicenter OLE study evaluated long-term dupilumab treatment in adults previously in phase 1-3 dupilumab AD trials
  › analysis examined pts given 300mg dupilumab wkly up to 76 wks at data cutoff: safety primary outcome; efficacy was also evaluated

› Of 1,491 enrolled pts (1,042.9 patient-years), 92.9% remained on treatment at cutoff
  › safety profile was consistent with previously reported trials with no new safety signals
  › sustained improvement seen up to 76 wks in all efficacy outcomes including measures of skin inflammation, pruritus and quality of life

› Safety and efficacy profile from this study supports role of dupilumab as continuous long-term treatment for patients with moderate-to-severe AD

U.S. dupilumab trials in adolescents & children with AD

› Efficacy and safety of dupilumab in patients ≥12 to <18 years of age with moderate-to-severe atopic dermatitis (NCT03054428) – FDA approved 03/2019

› Study to determine safety and tolerability of dupilumab with TCS in patients aged 6 to 11 years with severe atopic dermatitis (NCT03345914) – completed

› Safety, pharmacokinetics and efficacy of dupilumab in patients ≥6 mo to <6 yrs with severe AD (Liberty AD PRESCHOOL) (NCT03346434) – recruiting
Efficacy and safety of dupilumab in adolescents with uncontrolled moderate to severe atopic dermatitis: A phase 3 randomized clinical trial

**Figure:**

- **LS mean percentage change in Eczema Area and Severity Index score**
- **Mean percentage change in weekly average of Peak Pruritus Numerical Rating Scale score**

*a P<.0001 vs placebo*

JAMA Dermatol 2019; Nov 6 [Epub ahead of print]
Clinically meaningful responses to dupilumab in adolescents with uncontrolled moderate-to-severe atopic dermatitis: Post-hoc analyses from a randomized clinical trial

› 251 patients randomized

› Clinically meaningful responses defined (composite endpoint): 
  ≥50% improvement in EASI, or Peak PNR Scale score improvement ≥3, or CDLQI improvement ≥6 from baseline

› Clinically meaningful responses vs placebo seen at all time points 
  (wks 2, 4, 8, 12 and 16, \( P<0.0001 \) for q4w/q2w vs placebo at all time points, \( P<0.001 \) for q2w at wk 2) with 63.1% and 81.7% dupilumab q4w and q2w patients vs 25.9% placebo patients achieving composite endpoint at wk 16

Am J Clin Dermatol 2019 Dec 10 [Epub ahead of print]
Mechanism of action for biologics targeting the IL-4 and/or IL-13 pathways

Other biologics

› Anti-IL-13
  › Tralokinumab & lebrikizumab – phase 2 trials in combination with TCS not very effective (c/w placebo + TCS) – further studies ongoing or planned

› Anti-IL-31 receptor A (nemolizumab) – Phase 3 recruiting

› Anti-TSLP (tezepelumab) – Phase 2b recruiting

ClinicalTrials.gov
JAK-STAT signaling as a therapeutic target

Selectivity of JAK inhibitors

JAK usage and putative relationship to adverse events

Gadina M, et al. Rheumatology 2019;58:i4
JAK inhibitors in AD

› Clinical trials evaluating both oral and topical JAK inhibitors in treatment of AD ongoing
  › Oral: Baricitinib (Jak 1/2) completed phase 3 trials
    › compared to pts treated with placebo, statistically significant proportion of pts treated with baricitinib achieved primary endpoint at Wk 16 (IGA 0,1)
    › no venous thromboembolic events, major adverse cardiovascular events or deaths reported
  › Abrocitinib (Jak 1), upadacitinib (Jak 1) are currently in phase 3 trials
    › Upadacitinib phase 1 trial down to age 2 years
    › Upadacitinib and abrocitinib comparative studies with dupilumab
  › Topical: Ruxolitinib (Jak 1/2) in phase 3 trials, delgocitinib (pan-JAK) phase 2b
    › Abrocitinib and upadacitinib granted Breakthrough Therapy designation by FDA for AD
Safety of JAK inhibitors

› Most safety data comes from clinic trials of tofacitinib or baricitinib in patients with rheumatoid arthritis
› Patients treated with concomitant methotrexate with or without nonsteroidal anti-inflammatory drugs and glucocorticoids
› Box warning for serious infections, malignancy and thrombosis
› FDA warns of risk for PE, death with higher dose tofacitinib (10 mg bid) in patients with RA (Feb 25, 2019); new warning Jul 26, 2019 re increased risk blood clots & death with 10 mg bid tofacitinib
› ? Will new Jakinibs inherit boxed warning?
› ? Will Jakinibs be used as short term oral/topical intervention (AD tends to relapse quickly when D/C’d) and titrated to lowest effective dose
Successful treatment of atopic dermatitis with the JAK1 inhibitor oclacitinib

› Patient in his 70s with 6-year history of skin disease refractory to topical and biologic therapies (topical corticosteroids, topical and oral antihistamines and a trial of omalizumab)
› Self-prescribed this veterinary medication which resulted in significant reduction of erythema and itch within 2 hours of first administration
› Reports 7 months of continuous therapy, taking an oral dose of 0.12mg/kg q AM and 0.32mg/kg qhs
› Has remained in remission for 7 months with no reported adverse side effects or infections

Haugh IM, et al. Proc (Bayl Univ Med Cent) 2018;31:524
Targeted therapies and their applicability for specific AD endotypes and phenotypes


<table>
<thead>
<tr>
<th>Agent</th>
<th>Target</th>
<th>Phase</th>
<th>Manufacturer</th>
<th>Endotype targeted</th>
<th>AD phenotype</th>
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Clinical Management Review

Strategies for Successful Management of Severe Atopic Dermatitis

Kanwaljit K. Brar, MD, Noreen H. Nicol, PhD, RN, FNP, and Mark Boguniewicz, MD

Denver, Colo

J Allergy Clin Immunol Pract 2019;7:1-16
Annotated approach to the patient with severe AD

*e.g., Hanifin & Rajka, UK Working Party, AAD Consensus. †See Table II. e.g., clinician evaluation (IGA, SCORAD, EASI) and/or patient-reported (AD global assessment, PO-SCORAD) (see Table I). § Onset, course, area involved, suspected triggers, complications (e.g., infections), hospitalizations, associated atopic and nonatopic comorbidities, previous treatment including What? How much? and Where? IISee Fig. 2. (NJH AD Action Plan).
{Consider biopsy, patch testing, genetic testing. #FDA approved for patients 18 years or older with moderate-to-severe AD not adequately controlled with topical steroid or when topical steroid not indicated. Document severe AD, body surface area greater than 10%, previous therapies. **CSA, MTX, MMF, AZA. ††While FDA approved, systemic corticosteroids should be avoided or used for shortest course possible, usually while transitioning to a systemic therapy with slower onset of action.

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Additional information and references can be found in the referenced literature. For detailed guidance, please consult the referenced articles and guidelines for comprehensive management of severe AD.
Practical pearls for managing severe AD

- Participate in shared decision making with the patient and/or caregiver
  - Spend time listening to the patient and/or caregiver
  - Understand the patient’s goals and expectations (less itching, clearer skin, better sleep, other quality-of-life issues)
  - Clarify current medications and which ones are succeeding or failing
  - Give treatment options explaining the risks and benefits of these treatments
  - Consider all of the patient’s socioeconomic factors and ability to adhere with treatment recommendations (insurance, affordability, reimbursement, patient’s daily schedule, and work/school/family obligations)

- Explain the nature of the disease
  - Realize that deterioration in previously stable AD may result from secondary bacterial or viral infection, development of contact allergy, poor understanding or adherence to recommended treatment

- Clarify the severity of the patient’s AD
  - Explain how much body surface area is involved—more than 10% of the body is considered moderate-to-severe AD
  - Understand the extent or significant impact on quality of life (social, emotional, school, or professional functioning)

- Work to find the right treatment plan and individualize for the patient to promote adherence to agreed plan
  - Explain the role of proper skin hydration and moisturizers as daily care regardless of other treatments
  - Prescribe, as appropriate, TCSs and TCIs after taking into account patient’s age, site to be treated, extent/severity of disease, being sure to prescribe adequate amounts
  - Clarify patient’s vehicle preference for moisturizers and topicals
  - Demonstrate how to apply topical agents
  - Address steroid phobia or underuse if appropriate
  - Provide written recommendations regarding skin care including bathing and medicines including prescription and over-the-counter products including WPT
  - Consider use of biologics or phototherapy if failing conventional topical treatments, as appropriate
  - Consider use of other systemic therapies if failing other treatments
  - Prescribe, as appropriate, oral sedating antihistamines, topical and/or oral antimicrobials

- Provide patient education materials and additional support measures
  - Give patient education materials that support the specific messages and recommendations you are providing—not all do!
  - Consider structured educational interventions (eczema school, online programs, or patient support and advocacy groups)
  - Recommend environmental measures to avoid skin irritants and proven allergens or triggers
  - Recommend psychosocial support
  - Review skin care and reinforce key messages at follow-up visits

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NIAID Atopic Dermatitis Research Network
Protocol 09: Effect of dupilumab (anti-IL4Rα) on the host-microbe interface in AD

› Multi-center randomized double-blind, placebo-controlled trial investigating effect of 6 wks of dupilumab treatment on quantitative and qualitative measures of cutaneous microbial community structure, skin barrier biology, and circulating T cell profiles, followed by a 10 week open-label extension