Atopic Dermatitis

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Disclosure

• Consultant/Advisory Board: Anacor Pharmaceuticals, Galderma Laboratories, Johnson & Johnson, Merck & Co, National Eczema Association

• Speaker: Johnson & Johnson

• Honorarium: Anacor Pharmaceuticals, Galderma Laboratories, Johnson & Johnson, Merck & Co
Learning Objectives

Upon completion of this session, participants should be able to:

- Recognize the role of epidermal barrier abnormalities in atopic dermatitis
- Discuss key immunopathologic abnormalities in atopic dermatitis
- Prescribe treatments from the 4 key therapeutic categories
Big Problem

- AD is the most common chronic skin disease of young children, but can affect any age.
- Global health problem in developed and developing countries.
- Data from the 2003 National Survey of Children’s Health showed eczema prevalence in children 17 years and younger ranging by state from 8.7-18.1%.

QOL

- AD is an important cause of school absenteeism and occupational disability and impacts significantly on patient/family QOL.

- Sleep disruption is a major problem for patients and families (~2.6 h/night), even in remission.

Distribution at Various Ages

Natural History

- AD generally presents in early childhood with onset < 5 yrs in 90%

- In adults with new-onset AD, other diseases must be considered
Differential Diagnosis

Congenital disorders:
  • Netherton Syndrome

Immunodeficiencies:
  • Wiskott-Aldrich syndrome
  • SCID
  • Hyper-IgE syndrome
  • ID with DOCK8 mutations (hyper IgE)
  • IPEX (Immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome)
Differential Diagnosis

Infections and Infestations

• Scabies
• HIV-associated dermatitis

Malignancy

• Cutaneous T cell lymphoma (mycosis fungoides/Sézary syndrome)

Proliferative Disorders

• Letterer-Siwe disease (LCH)
Differential Diagnosis

Metabolic Disorders

• Zinc deficiency
• B6 (Pyridoxine) and niacin deficiency
• Multiple carboxylase deficiency
• Phenylketonuria
Differential Diagnosis

Other Dermatoses

- Seborrheic dermatitis
- Contact dermatitis
- Nummular eczema
- Lichen simplex chronicus
CTCL

- Epidermotropic neoplasm of CD4+ T cells
- Has several variants and may be mistaken for dermatitis
- “Parapsoriasis” (sometimes called ‘chronic superficial scaly dermatitis’) is possibly a milder variant of CTCL and is often mistaken for it
- Skin biopsy is essential here, and referral to experienced dermatologist
Seborrheic Dermatitis
Zinc Deficiency
Scabies
DOCK8 Mutations

- Deducator of cytokinesis 8 encodes protein that helps regulate actin cytoskeleton
- Increased viral infections (HSV, warts, molluscum)
- Decreased CD4+ and CD8+ T cell activation
- Dysregulation of IgE
- Eczema
- Often the cause of AR HIE syndrome
- (Job syndrome is STAT3 mutation)
DOCK8

- Eczema
- Warts
- Molluscum

Ichthyosis Linearis Circumflexa (Netherton)
Nummular
IPEX Syndrome

- Immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome
- Rare
- Associated with: dermatitis, type 1 diabetes, enteropathy, thyroiditis, hemolytic anemia, and thrombocytopenia
- Mutation of FOXP3 gene (T cell regulatory protein)
IPEX

Testing
WHAT ABOUT FOOD?
WHAT ABOUT FOOD?

- Some 30% of patients with moderate to severe eczema have true food allergies.
- However, there is a poor correlation between specific IgE blood tests and skin prick tests, and clinically significant reactions.

**WHAT ABOUT FOOD?**

- Patient and family reports of food allergies should be confirmed, because 50 to 90 percent of presumed food reactions are not actually clinically significant allergies.

- In one longitudinal study, positive specific IgE tests were seen in 63 to 74 percent of patients, but only 24 to 37 percent of these same patients had clinically significant food reactions.

WHAT ABOUT FOOD?

- New guidelines were coordinated by the National Institute of Allergy and Infectious Disease, and will be coming out soon. They will suggest:

- Testing for food allergies in eczema ONLY in those patients who have a history suspicious for food reactions OR

- In moderate to severe persistent atopic dermatitis patients who are not responding to standard therapies, AND are less than five years of age

Food Allergens

- May exacerbate disease in certain patients
- 7 foods (milk, egg, peanut, soy, wheat, fish and nuts) account for about 90% of all positive challenges
Aeroallergens

- Somewhat controversial that dust mite avoidance can result in clinical improvement of AD

- However, respiratory route and skin contact with aeroallergens may play a role yet
What is AD?

- Impaired skin barrier function
- A proinflammatory atopic response to antigens
- Reduced cutaneous antimicrobial activity
- Abnormal itch response

- Because these main factors and their molecular pathways interact and potentiate each other, optimal AD management addresses all simultaneously
Fig. 50. Atopic dermatitis. Principal etiologic and contributory factors.
Complicating features of AD

- Increased susceptibility to infections or colonization (staph, HSV, malassezia)
- Atopic keratoconjunctivitis present with ocular pruritus may result in visual impairment from corneal scarring
- Hand dermatitis aggravated by wetting repeatedly; may lead to occupational disability
Severe Hand Dermatitis
Moisturization
Skin barrier
FILAGGRIN

- Mutations cause ichthyosis vulgaris (IV)
- 8% of eczema pts have features of IV
- Between 14 and 56% of eczema pts carry one or more filaggrin null mutations

IL-4 AND IL-13

Keratinocytes differentiated in the presence of IL-4 and IL-13 exhibited significantly reduced filaggrin gene expression

Filaggrin

- Loss of function mutations strongly associated with AD and asthma occurring in context of AD
- Not present in the bronchial epithelium, however
- Percutaneous priming or secondary immunological effects may be mechanism in airway disease

Beyond Filaggrin

- Abnormalities in epidermal protein function have been identified in:
  - Loricrin
  - Involucrin
  - Hornerin

- Also abnormal in *nonlesional* skin

- All are downregulated in response to the Th2 cytokines known to be elevated in AD


Not sufficient...

- An abnormality in epidermal barrier alone is not sufficient for development of AD, since even patients homozygous for filaggrin null mutations do not always develop dermatitis and may clinically outgrow the disease.

Vicious Cycle

- Impaired barrier permits increased entry of microbes, antigens/irritants, increased water loss
- \( \rightarrow \) Proinflammatory \( T_H^2 \) cytokine environment
- \( T_H^2 \) response mediated by IL-25, IL-33 and thymic stromal lymphopoietin (TSLP) released by barrier-disrupted epidermis or tissue injury \( \rightarrow \) the eosinophilia and elevated IgE characteristic of AD and systemic allergic responses


MOISTURIZERS

- Greasier is probably better
- But adherence can be lower
- Fancy new preparations (lipids, ceramides, etc) not shown to be better than older, simpler products
More moisturizer use correlates with less eczema!

Cork et al. BJD 2003; 149: 582-589.
TREATMENT

- Anti-inflammatory
- Antibiotics
- Antipruritics
- Moisturization
Thymic stromal lymphopoietin (TSLP)

- Cytokine expressed by keratinocytes in AD
- Can activate dendritic cells (DCs) and induce production of TH2 cell-attracting chemokines
- Naïve CD4+ T cells can be primed by TSLP to differentiate into Th2 lymphocytes
Cytokines

- Acute inflammation is associated mostly with IL-4 expression, whereas chronic inflammation is most associated with IL-5 and eosinophil infiltration.
- IL-13 expression is higher in acute lesions.
- Increased IFN-gamma expression in chronic AD as well.
- IL-31 associated with inflammation and pruritus as well as overall disease activity in AD.
- Staph superantigens appear to induce IL-31.

ANTI-INFLAMMATORY

- Topical steroids are mainstay of treatment
- Ointments generally preferred
- Hard to do damage in < 2 weeks
- The risks (atrophy, striae, dyspigmentation, hypertrichosis) must be weighed against the benefits...
Table 1  Potency Ranking of Some Commonly Used Topical Corticosteroids

<table>
<thead>
<tr>
<th>CLASS</th>
<th>GENERIC NAME</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very High Potency I</td>
<td>Betamethasone dipropionate-augmented 0.05% - Oint</td>
</tr>
<tr>
<td></td>
<td>Clobetasol propionate 0.05% - Cream and Ointment</td>
</tr>
<tr>
<td>High Potency II</td>
<td>Betamethasone dipropionate 0.05% - Ointment</td>
</tr>
<tr>
<td></td>
<td>Desoximetasone 0.25% - Cream</td>
</tr>
<tr>
<td></td>
<td>Fluocinonide 0.05% - Cream and Ointment</td>
</tr>
<tr>
<td></td>
<td>Mometasone furoate 0.1% - Ointment</td>
</tr>
<tr>
<td>III</td>
<td>Betamethasone dipropionate 0.05% - Cream</td>
</tr>
<tr>
<td></td>
<td>Betamethasone valerate 0.1% - Ointment</td>
</tr>
<tr>
<td></td>
<td>Fluticasone propionate 0.005% - Ointment</td>
</tr>
<tr>
<td>Mid-Potency IV</td>
<td>Fluocinolone acetonide 0.025% - Ointment</td>
</tr>
<tr>
<td></td>
<td>Mometasone furoate 0.1% - Cream</td>
</tr>
<tr>
<td></td>
<td>Triamcinolone acetonide 0.1% - Cream</td>
</tr>
<tr>
<td>V</td>
<td>Betamethasone valerate 0.1% - Cream</td>
</tr>
<tr>
<td></td>
<td>Fluocinolone acetonide 0.025% - Cream</td>
</tr>
<tr>
<td></td>
<td>Fluticasone propionate 0.06% - Cream</td>
</tr>
<tr>
<td>Low Potency VI</td>
<td>Alclometasone dipropionate 0.05% - Ointment</td>
</tr>
<tr>
<td></td>
<td>Clobetasol butyrate 0.05% - Cream</td>
</tr>
<tr>
<td></td>
<td>Desonide 0.05% - Cream and Ointment</td>
</tr>
<tr>
<td>VII</td>
<td>Hydrocortisone or hydrocortisone acetate 1% - Cream and Ointment</td>
</tr>
<tr>
<td></td>
<td>Hydrocortisone acetate 0.127% - Cream</td>
</tr>
</tbody>
</table>

Adapted From: Pocket Guide TO MEDICATIONS USED IN DERMATOLOGY
The vasoconstrictor assay was developed in the 60s (Stoughton, 1962) and is very useful. Although it uses only one aspect of the drug, it correlates well with clinical effectiveness.
Topical Steroids

• Hard to do damage in < 2 weeks
• The risks (atrophy, striae, dyspigmentation, hypertrichosis) must be weighed against the benefits...
MAINTENANCE THERAPY

- Maintenance tacrolimus twice weekly when eczema clear
- Was effective in reducing the number and frequency of disease exacerbations and improving health-related QoL

Twice weekly tacrolimus

Microbes

- AD patients are more vulnerable to infections from staphylococcus, herpes simplex and molluscipoxviruses

- This is in part due to innate immune deficiencies in AD skin as well as the reduced epidermal barrier function resulting from the $T_H^2$ cytokine milieu and primary filaggrin defects, including impaired TLR function


Severe atopic dermatitis is associated with a high burden of environmental Staphylococcus aureus

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Summary

Background About 90% of patients with atopic dermatitis (AD) are colonized with Staphylococcus aureus. S. aureus worsens AD by secreting superantigens and structural molecules within the cell wall that induce skin inflammation. Therefore, S. aureus in the home may contribute to persistent skin inflammation and disease severity.

Objective To quantify S. aureus burden in homes of participants with AD of varying severities.

Methods Participants with mild (n = 18), moderate (n = 14), severe (n = 15), and no AD (n = 15), collected dust from their bed and bedroom floor, and from their home vacuum cleaner bag. DNA was extracted from dust samples, and the S. aureus-specific femB gene was quantified using quantitative real-time PCR. Data was log-transformed, and then statistically analysed with ANOVA, student’s t-test, and Spearman’s r.

Results Participants with severe AD (geometric mean: 14.67 pg/mg dust) had significantly more S. aureus DNA in their bed dust than those with moderate [0.41 pg/mg dust, P < 0.0001], mild [1.42 pg/mg dust, P = 0.0051], and no AD [0.09 pg/mg dust, P < 0.0001] (t-test). Similar patterns were observed for dust from the bedroom floors and vacuum bags. S. aureus DNA was highest in dust from beds as compared with bedroom floors or vacuum bags (medians: 1.51, 0.69, 0.21 pg/mg dust, respectively; P = 0.007). Eczema Area and Severity Index scores correlated with S. aureus DNA from the bed (Spearman’s r = 0.7263; P = 0.0004) and floor (0.6946; P = 0.0002) dust, but not with the vacuum bag dust (0.3783; 0.0684).

Conclusions In the home and especially the bedroom, higher levels of S. aureus may contribute to disease severity and persistence in AD patients.
Staph

- >80% of AD patients have toxin-producing staph on the skin
- May make specific IgE antibodies to toxins on skin
- Increased colonization may be associated with decreased antimicrobial peptides (defensins and cathelicidins), a defect in innate immunity mediated by IL-4 and IL-13

J Allergy Clin Immunol 2000;105:860
J Allergy Clin Immunol 2006;118
Eczema Vaccinatum

- Beyond eczema herpeticum
- Household transmission can occur

FIGURE. Abdomen and chest of a boy aged 28 months with a rash of umbilicated lesions caused by eczema vaccinatum — United States, 2007

Household transmission of vaccinia virus from contact with a military smallpox vaccinee --- Illinois and Indiana, 2007
MMWR, May 18, 2007
Vitamin D

- AD patients may be deficient in defensins and cathelicidins
- This may allow enhanced colonization
- Oral D3 can induce cathelicidin production

*J Allergy Clin Immunol* 2006; 118
Ong PY, et al. *NEJM* 2002; 347; 1151
I I children (mean age, 7 years) w/ AD that worsened in winter

Randomly given 1000 IU of D2 or placebo qd x 1 mo

Otherwise normal regimen

VITAMIN D

<table>
<thead>
<tr>
<th>Change in IGA score</th>
<th>Vitamin D</th>
<th>Placebo</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>+1 (worse)</td>
<td>–</td>
<td>1 (17%)</td>
<td>1</td>
</tr>
<tr>
<td>0 (same)</td>
<td>1 (20%)</td>
<td>4 (67%)</td>
<td>5</td>
</tr>
<tr>
<td>−1 (better)</td>
<td>4 (80%)</td>
<td>1 (17%)</td>
<td>5</td>
</tr>
<tr>
<td>Total</td>
<td>5</td>
<td>6</td>
<td>11</td>
</tr>
</tbody>
</table>

VITAMIN D?

- A + D Ointment may also make it worse: Thymic stromal lymphopoietin (TSLP) is an IL-7-like cytokine that triggers Th2 inflammatory responses and may be a master regulator of AD inflammation.

- Application of vitamin D ligands (calcitriol or calcipotriol) induces TSLP in keratinocytes which results in atopic dermatitis-like syndrome.

- Application of retinoic acid receptor (RAR) agonists also induces TSLP alone and synergistically with D3.

Feily A, Namazi MR. Vitamin A + D ointment is not an appropriate emollient for atopic dermatitis. Dermatitis. 2010 Jun;21(3):174-5
ANTIBIOTICS

- Oral (e.g., cephalexin, diclox)
- Mupirocin
- Castellani’s Paint (!)
- Bleach...
Dilute Bleach baths

- Randomized, investigator-blinded, placebo controlled study of 31 children with moderate to severe eczema
- All received oral antibiotics
- Half also got intranasal mupirocin and dilute bleach bath; Other half got vaseline + placebo bleach
- Decreased the clinical severity of eczema significantly at 1 and 3 month visits

TREATMENT

- Anti-inflammatory
- Antibiotics

Moisturization

Antipruritics
Itch

• AD patients experience neuronal sensitization and increased epidermal innervation
• More prone to itch and discomfort

ANTIPRURITICS

- Pramoxine, calamine, menthol, or camphor—minimally helpful
- Hydroxyzine or cetirizine
- Sedation may be of use at night
- Mirtazapine (TCA)
- But antihistamines probably not that helpful

Thank you!

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