Atopic Dermatitis in Infancy and Childhood

U. Wahn
Berlin, Germany
The atopic infant
MAS birth cohort: Multicenter Allergy Study

n = 1314  1/3 with high CB-IgE and/or atopy in the family

IgE-Ab vs mites, cat, dog, grass, birch
milk, egg, soy, wheat
total IgE

- telephone interview
- id. + direct exam + blood drawing
- lung function test
- bronchial provocation test
  (histamine/cold air)

1990

1990

birth 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20

environmental controls

age (years)
Prevalence of atopic eczema during the last 12 months according to age and sex

Grabenhenrich et al; in preparation
### Early life predictors of eczema

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Hazard Ratio</th>
<th>CI (Wald)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atopy in family</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 or 2 vs. 0 atopic parents</td>
<td>1.35*</td>
<td>[1.05;1.73]</td>
</tr>
<tr>
<td>Early sensitization</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 0.35 kU/l sensitized vs. Not sensitized</td>
<td>2.67**</td>
<td>[2.02;3.53]</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>male vs. female</td>
<td>1.03</td>
<td>[0.81;1.31]</td>
</tr>
<tr>
<td>Education</td>
<td></td>
<td></td>
</tr>
<tr>
<td>low vs. medium/high</td>
<td>0.68</td>
<td>[0.48;0.96]</td>
</tr>
<tr>
<td>Living environment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>village vs. city</td>
<td>0.77*</td>
<td>[0.55;1.08]</td>
</tr>
<tr>
<td>Age of mother</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;25 vs. &gt;= 25 years</td>
<td>0.83*</td>
<td>[0.56;1.24]</td>
</tr>
<tr>
<td>Cord blood cotinin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;=5 vs. &lt;5 ng/ml</td>
<td>0.96*</td>
<td>[0.65;1.40]</td>
</tr>
</tbody>
</table>

* adjusted for educational status of parents,  ** for all other factors,  proportional Hazards (PH) model, CI: 95% confidence interval
Eczema: new onset in last 12 months

Incidence [per year]

- Boys
- Girls

Age [years]:
- 0-1
- 2-3
- 4-5
- 5-10
- 10-15
- 15-20

Percentage:
- 0%
- 2%
- 4%
- 6%
- 8%
Eczema: prognosis by age at onset

- Onset in...
  - 1st year: 30% remaining at 20y...
  - 2nd year: 26% remaining at 20y...
  - 3rd year: 21% remaining at 20y...
  - 4th year: 20% remaining at 20y...
  - 5th year: 10% remaining at 20y...

At birth n=1314

MAS – birth cohort (Germany)
Eczema and atopic status

- multi-sensitized (first 3y)
- mono-sensitized (first 3y)
- not sensitized (first 3y)

non-adjusted Kaplan-Meier-curves
Infantile skin barrier and the role of emollients for prevention.

Barrier Defect

Allergens
Viridae, Bacterias

Sensitization
Inflammation
Persistant Infection

Filaggrin
Gene Defect
The skin in atopic dermatitis children

- reduced content of water and fat
- disturbed sweat regulation
- hyperreactivity to mechanical and chemical irritants
- reduced resistance to infection
- susceptibility to inflammation

Palmer, CN et al, Nat Genetics, 2006, 38, 441-446
T cells in skin lesions of atopic dermatitis

Kindly provided by Professor G Stingl, Vienna, Austria
Diagnostic steps in atopic dermatitis

Diagnostic criteria?

Severity (SCORAD)

- Food allergy
  - Specific IgE
    - DBFCFC
- Superinfection
  - culture
- Allergy to aeroallergens
  - Specific IgE
Patient’s self-management action plan

Exacerbation strategy
Mid-potency topical steroids
Uncontrolled disease:
↑ Potency of topical steroid

Early intervention strategy
Elidel bid
at first signs or symptoms

Maintenance strategy
Avoidance/emollients
Conventional Treatment Strategy

**DISEASE SEVERITY**

- Dry skin
- Itching and/or early signs of inflammation
- Severe Flare

**TREATMENT**

- Emollients
- Topical steroids
Proportions of infants who did not have AD/eczema

AD: Regular treatment with emollients

• Improvement of barrier function
  Breternitz et al, Skin Pharmacol Physiol 2008, 21, 39-45
  Verallo-Rowell et al, Dermatitis 2008, 19, 308-15

• Steroid sparing effect
  Grimali et al. Dermatology 2007, 214, 611-67
  Szczepanowska et al. PAI 2008, 19, 614-8
Antiinflammatory Treatment:

Steroids: Different potencies - different risks

Calcineurin-Inhibitors: Tacrolimus, Pimecrolimus
# Topical Corticosteroids

## Potency Ranking (Miller & Munro)

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Trade Name</th>
<th>Concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clobetasol-17-propionat</td>
<td>Dermoxin</td>
<td>0.05%</td>
</tr>
<tr>
<td>Diflucortolon-21-valerat</td>
<td>Temetex forte Roche</td>
<td>0.3%</td>
</tr>
</tbody>
</table>

---

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Trade Name</th>
<th>Concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amcinonide</td>
<td>Amciderm</td>
<td>0.1%</td>
</tr>
<tr>
<td>Betamethason-17,21-dipropionate</td>
<td>Diprosone</td>
<td>0.05%</td>
</tr>
<tr>
<td>Betamethason-17-valerat</td>
<td>Betnesol, Celestan</td>
<td>0.1%</td>
</tr>
<tr>
<td>Desoximetasone</td>
<td>Topisolon</td>
<td>0.25%</td>
</tr>
<tr>
<td>Diflucortolon-21-valerat</td>
<td>Nerisona</td>
<td>0.1%</td>
</tr>
<tr>
<td>Fluocinolone acetonide</td>
<td>Jellin</td>
<td>0.025%</td>
</tr>
<tr>
<td>Fluocinolone</td>
<td>Topsym</td>
<td>0.05%</td>
</tr>
<tr>
<td>Fluocortolone</td>
<td>Ultralan</td>
<td>0.5%</td>
</tr>
<tr>
<td>Fluorprednisolone-21-acetate</td>
<td>Decoderm</td>
<td>0.1%</td>
</tr>
<tr>
<td>Halcinonide</td>
<td>Halog</td>
<td>0.1%</td>
</tr>
<tr>
<td>Hydrocortisonaceponate</td>
<td>Retef</td>
<td>0.1%</td>
</tr>
<tr>
<td>Hydrocortisonbuterate</td>
<td>Pandel</td>
<td>0.1%</td>
</tr>
<tr>
<td>Hydrocortison-17-butyrate</td>
<td>Alfason</td>
<td>0.1%</td>
</tr>
<tr>
<td>6-Methylfluorprednisolone aceponate</td>
<td>Advantan</td>
<td>0.1%</td>
</tr>
<tr>
<td>Metamizone</td>
<td>Ecural</td>
<td>0.1%</td>
</tr>
<tr>
<td>Prednicarbate</td>
<td>Dermatop</td>
<td>0.25%</td>
</tr>
<tr>
<td>Triamcinolone acetonide</td>
<td>Delphicort, Volon A</td>
<td>0.1%</td>
</tr>
</tbody>
</table>

---

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Trade Name</th>
<th>Concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clobetasonbutyrate</td>
<td>Emovate</td>
<td>0.05%</td>
</tr>
<tr>
<td>Cloclorolone-21-pivalate</td>
<td>Kaban</td>
<td>0.1%</td>
</tr>
<tr>
<td>Fluocortinbutyl</td>
<td>Vaspit</td>
<td>0.75%</td>
</tr>
<tr>
<td>Flumethasone-21-pivalate</td>
<td>Locacorten</td>
<td>0.02%</td>
</tr>
</tbody>
</table>

---

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Trade Name</th>
<th>Concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrocortison</td>
<td>Ficortexil</td>
<td>0.1-1%</td>
</tr>
</tbody>
</table>
Corticosteroids: Therapeutic Index (TIX)
(Quotient: Efficacy/Adverse Events)

Efficacy
(Vasoconstriction, Anti-inflammatory)

Adverse Events
(Atrophy, HPA ↓, Allergenic Potency)

MPA leads to a significantly lower intensity of itch during the maintenance phase

- Intensity of itch remained stable over the course of the maintenance phase

Short-Term Efficacy of MPA

- MPA leads to rapid relief of symptoms: complete or near complete clearing of atopic dermatitis lesions occurred in 2/3 of patients.

- Both treatment groups were efficacious, nevertheless more patients treated with MPA had completely cleared symptoms by the end of treatment (37.2% MPA vs 29.4% tacrolimus).

- MPA was superior to tacrolimus for EASI, itch relief and quality of sleep.

- MPA shows excellent tolerability.

Bieber T et al, Allergy 2007;62:184-9
Structural differences between Pimecrolimus und Tacrolimus

- **Pimecrolimus**
  - **hydroxy**
  - **Doppelbindung**

- **Tacrolimus**
  - **epi-chloro**
  - **keine Doppelbindung**
Calcineurin inhibitors - mechanism of action

Calcineurin Inhibitors
- Cyclosporin A
- Tacrolimus
- Pimecrolimus

Macrophilin-12

Pimecrolimus
Tacrolimus

Minimal Increase in Blood Concentrations with Rising % BSA Treated

$r^2 = 0.08$

Difference in mean blood concentration for infants with 90% BSA and 10% BSA is 0.5 ng/ml

Lakhanpaul et al. AAD2002
In children pimecrolimus is particularly effective in treating AD of face and neck.

Median change EASI from baseline (%)

- Vehicle face/neck
- Vehicle overall
- Elidel overall
- Elidel face/neck

Days

Baseline 8* 15 22 29 43

*Day 8 = first scheduled visit

Cyclosporin A (Neoral®, CyA)

- Wirkung: Hemmung der T-Zellaktivierung über Calcineurin/NFAT
- Orales CyA bei entzündlichen Hauterkrankungen hocheffektiv
- Topisches CyA unwirksam
Cyclosporin in Severe Atopic Dermatitis

**Graph Description:**
- **Y-axis:** Sleep disturbance
- **X-axis:** Weeks (-2 to 12)
- Data is divided into two groups: on cyclosporin (red) and off cyclosporin (yellow).
- Significant differences are marked with asterisks: 
  - ** *** at 0 weeks
  - ** ** at 2 weeks

**Graph Analysis:**
- Sleep disturbance is highest at 0 weeks for both groups.
- There is a notable decrease in sleep disturbance from weeks 2 to 12 for both groups.
- The graph indicates a significant improvement in sleep disturbance over time for both groups.
Education is essential!

Staab, D; Diepgen, TL et al

„Age related structural educational programmes for the management of atopic dermatitis in children and adolescents: multicentre randomized controlled trial.“

BMJ 2006, 332, 933-8
Neurodermitis Elternschulung

Universitätskinderklinik der Humboldt-Universität zu Berlin
Children with atopic dermatitis and their parents need more than emoilllients, creams, and drugs!

-Instruction by nurses
-structured educational programs for children and caregivers
Thank you for attention!
Prevention?
Principles of Reducing Allergenicity

Whole protein
Moderately hydrolyzed
Highly hydrolyzed
Extensively hydrolyzed
Amino acids

Cows milk protein
Beba HA
Humana HA
Milumil HA
Aptamil HA
Hipp HA
Alfaré
Nutramigen
Pregomin
Althera
Neocate
Pregomin AS

Allergenicity
Prebiotic, Probiotic and Synbiotic Food

- **Probiotics**: Living bacteria in the food
  - % survival?
  - Activity?
  - Excretion

- **Synbiotics**: Combination of Probiotics and Prebiotics
  - Active exogenous bacteria
  - Promotion of active endogenous beneficial bacteria

- **Prebiotics**: Neutral HMOS (GOS/FOS)
  - Fermentation in the colon