Conflicts of Interest:

- Graceway PI, speaker
- Pierre Fabre I, speaker
- Roche Posay grant, speaker
- Celgene
- Pfizer ad board
- Valeant ad board; speaker
- Galderma
- Janssen ad board,
- Abbvie speaker
- Novartis speaker
Objectives

- Adherence - Compliance
- Be sure it is Atopic dermatitis
- How to manage your patients, go-to systemic agents and biologics like dupilumab/omalizumab
Pathogenesis: Immune Dysregulation

FLG mutations
Other mutations
Lipid defects

pH changes
Irritants → Trauma/scratching

Proteases

Cytokines

Th2 cells

IL-4
IL-13

B cells

IL-31

JAK/STAT

Sensory neurons

TSLP

↑ PDE4
↓ cAMP

IgE

Itch

Silverberg J
A boy with severe generalized AD, multiple episodes of impetigo

Food allergies
Antibiotics
Antihistamines, clonidine
Cyclosporin
Adherence!

1/3 patients do not fill their prescriptions
2/3 that do: adherence is 32% after 8 weeks.

Used the corticosteroid ointment ‘sparingly’
Stopped once AD flared!!!
REDUCING FLARES IN A D

1. Emollients
2. Wet wraps
3. Corticosteroids
4. Calcineurin inhibitors

Food allergy in AD in infants

- 4 phenotypes of atopic dermatitis in childhood:
  - **early phenotypes**: onset before age 2 years. *early transient* [9.2%]
  - *early persistent* [6.5%])
  - **late phenotype**: onset at age 2 years or older (4.8%)
  - **never phenotype** (n = 825; 79.5%) no atopic dermatitis.
- Both early phenotypes strongly associated with food allergy.
- Chronological and dose-dependent associations between food allergy in adolescence & adult-onset AD.

Resistant Atopic Dermatitis

- Many topical corticosteroids
- Many emollients
- Tacrolimus 0.1% ointment
- For pruritus: Antihistamines Hydroxyzine 1 mg-kg hs; Doxepin, clonidine
- For Infection: Topical and oral anti-staph Antibiotics
- Cyclosporin 5 mg-kg-d
- Omalizumab 300 mg SC q 4 wks
- Consultation to allergist: RAST, skin prick tests
Resistant atopic dermatitis

- Patch tests:
  - Allergic contact dermatitis (ACD)
  - To propylene glycol:
    - PG is the most common (64%) allergen in topical corticosteroids
    - Systemic contact dermatitis to PG following oral ingestion of foods, capsules and intravenous Rx

Al Jasser M Skin Therapy Letter 2011
Jacobs S 2013
Take Away Message #1: SIMPLE

- Is there an allergen lurking at home?
Patch testing in atopic dermatitis

Patch test +

Propylene glycol

Fragrance

Cinnamate

Owen JL. The Role Diagnosis of Allergic Contact Dermatitis in Patients with AD. Am J Clin Dermatol. 2018 Jan
Refractory dermatitis in a 17-year-old Vietnamese girl

- Avoiding contact allergens and still not better
Before you start a systemic or biologic agent

- Be sure of the diagnosis
- Screen for malignancy, infections, collagenoses
- History of varicella, **hepatitis B & C, HIV, syphilis, TB**
  - CXR; Screen for latent TB: PPD, QuantiFERON gold
  - CBC, AST, ALT, ANA, if + ENA, ds-DNA
- Live vaccines up-to-date 1 month prior
- IgG if rituximab, lipids before tocilizumab
- Adolescent F: add ßHCG

RCN guidance_Biologics 2016
Live vaccines pre-biologics

When on a biologic:

- No live vaccines
- Influenza q yr,
- Pneumococcal vaccine q 5 yrs.
Take Away Message #2: Infections: TB, MRSA, Scabies

- Dermatitis 80% better 1 month after starting isoniazid
- So was this a tuberculid?
Atypical AD

- Nummular eczema
- History: Biopsy-proven Pityriasis Lichenoides Chronica
- Atypical hypopigmented patches
- Biopsy showed Mycosis Fungoides
- Patient did well on phototherapy nbUVB x 2 years, clear since
Take Away Message #3: BIOPSY
A 12-year-old girl with refractory AD

- Treated by her GP, several dermatologists in the last 11 months
- Family history of atopy in the father
- Given hydroxyzine and Desoximetasone 0.25% ointment, moisturizers
- Weight loss and fatigue 2 months prior to admission, BMI 13.7
A 12-year-old girl with refractory AD

- Atypical features:
  - No flexural accentuation.
  - Atopic dermatitis rarely begins after 4 years of age,
  - Refractory
  - Constitutional symptoms

- Painless 2 x 2-cm lymph node in the left supraclavicular area
- Dermopathic lymphadenopathy?
Investigation

- CBC:
  - WBC 9.6, Hb:104, plt:630
- Iron: 3.4↓
- Albumin: 30↓
- Sed: 50↑, CRP: 107↑
Diagnosis:

- Hodgkin’s Lymphoma stade IVB
- Secondary neurodermatitis (Hodgkin’s prurigo)
Hodgkin’s Prurigo

- Amy de la Bretèque M Ann Dermatol Venereol. 2014 ;141(12):765-8
Take Away Message #4: Systemic causes of Pruritus

- **Paraneoplastic itch** lymphoma, leukaemia or a solid organ tumour, *Mycosis fungoides*
- Metabolic disorders include chronic renal failure (dialysis) and liver disease (cholestasis).
- Haematological disorders include iron deficiency anaemia and polycythaemia vera.
- Endocrine disorders include thyroid disease.
- Infections causing itch include **HIV** and **hepatitis C virus**.
- **Pruritic skin diseases**
  - Dermatitis herpetiformis, Bullous pemphigoid, Lice, Scabies
- Medications (topical or systemic) eg opioids, aspirin
Pathophysiology of Atopic Dermatitis

Annals of Allergy, Asthma & Immunology 2018 120, 10-22 DOI: (10.1016/j.anai.2017.10.039)
Systemic agents used in AD

- Phototherapy
- Systemic corticosteroids,
- Cyclosporine (45.2%)
- Methotrexate (29.6%),
- Mycophenolate mofetil (13.0%).
- ±Azathioprine
Phototherapy in AD

- **narrowband UVB** first choice light therapy for chronic AD. (50-68% response)
- **MD-UVA1** radiation first choice for acute AD. If not available, substitute by full-spectrum UVA with satisfactory results.

**Problems:**
- Limited access to in-office treatment
- Difficulty adhering to 3x wk schedule
- Acute: sunburn, blisters, xerosis, flaring from excessive heat
- Increased risk of skin cancer
- Unable to treat scalp or genitals

Systemic Corticosteroids

- Limit the use of systemic steroids to short courses as a bridge to steroid-sparing therapies.
- That is the general consensus in the literature ((52 reviews and 12 studies).
- Optimal delivery or duration unknown
- Risk of rebound flare ++++

- What I do but SELDOM: Kenalog 1 mg-kg IM to a max of 50 mg or prednisone 1mg-kg q am x 5 days, and 0.5 mg-kg qam x 5 days as a stop gap while starting an immunosuppressive agent

Yu S+ A systematic review of safety efficacy of systemic corticosteroids in atopic dermatitis. JAAD 2017 Oct
Systemic Corticosteroids

- Rebound flaring.
- Adrenal suppression, Cushing syndrome
- ↓growth in children, weight gain,
- Hypertension
- Gastritis, gastroesophageal reflux, peptic ulcer disease
- Opportunistic infections
- Emotional lability, sleep disturbance
- Cataracts, glaucoma
- Myopathy, myalgia, dysesthesia, pseudotumor cerebri,
- Hyperlipidemia, glucose intolerance, diabetes
- Osteoporosis, osteonecrosis
- Thrombosis, malignancy

Yu S+ A systematic review of safety efficacy of systemic corticosteroids in atopic dermatitis. JAAD 2017 Oct
## Systemic immunosuppressors used in AD

<table>
<thead>
<tr>
<th>Drug</th>
<th>Average dose mg</th>
<th>mg/kg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mycophenolate mofetil</td>
<td>900</td>
<td>10-20</td>
</tr>
<tr>
<td>Mycophenolate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>200 mg</td>
<td>3-5</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>15-25 /wk</td>
<td>0.4-0.5</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>50-100 /d</td>
<td>2-3</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>50 /d</td>
<td>1-2</td>
</tr>
</tbody>
</table>

60 kg

Gerbens LAA. Methotrexate and azathioprine severe AD. Br J Dermatol. 2017 Dec

Newer agents for the treatment of Atopic Dermatitis
Competition for Biologics: Apremilast for Psoriasis & Atopic Dermatitis

- A phosphodiesterase inhibitor $\uparrow$ cAMP
- $\downarrow$ T cell activation

- PASI 75 in 33% of patients
- Safe, no blood tests
- Initially minor GI intolerance, risk of depression
- May surplant MTX, CyA in psoriasis
- Some benefit for arthritis
- 30 mg bid except renal insufficiency

Ritchlin CT, Curr Opin Rheumatol. 2016 May;28(3):204-10.
Phosphodiesterase 4 Inhibitors in AD Oral

Apremilast 30 mg bid in 5 patients; 2 patients >75% improvement, 1 >90%

Phosphodiesterase 4 Inhibitors in AD Oral

- Mechanism of action: ↓ proinflammatory cytokines
- No lab tests!
- Limited data: Apremilast 20 mg-30 mg bid - less effective than in psoriasis
- Pilot studies: Improvements in EASI scores and IGA 10% > 75%, 10% > 50%
- Awaiting a DB placebo controlled trial in 191 adults with AD 30-40 mg bid x 12 wks, then Xover (NCT02087943)
- Adverse effects: GI, headache
Phosphodiesterase 4 Inhibitors in AD Topical

Magnitude of benefit for topical crisaborole in the treatment of atopic dermatitis in children and adults does not look promising: a critical appraisal
Phosphodiesterase 4 Inhibitors in AD Topical

- Crisaborole 2% ointment, FDA-approved in 2016 USA for children >2yrs of age and adults in the treatment of AD.
- Early improvement in disease severity and pruritus however this was *clinically minimal significance*
- Short: 28 days, ~33% response vs ~25% for vehicle; ↓ pruritus 7.9h
- Safe, although 4.4 % local stinging

- Others under trial

Zebda R, Paller AS, JAAD(2018),
BIOLOGICS FOR ATOPIC DERMATITIS

Anti-IgE THERAPY

- Omalizumab: approved for resistant asthma in 2005 (EU) 2003 (US) & chronic spontaneous urticaria (CSU) in 2014 in ≥ 12 yrs
  - 150-375 mg q 2 asthma & 300 mg q 4 wks
  - Upper limits in patient weight:
    - USA 60 kg for maximum IgE 700 IU/mL
    - EU 50 kg for maximum IgE 1500 IU/mL

- 58 clinical trials in children registered for other indications (Lipari A Paed Drugs 2014)

- Other Anti-IgE are in trials: quilizumab, ligelizumab, MEDI4212*

Staubach P, ...Maurer M. Allergy. 2016 Mar 24. doi: 10.1111/all.12870. CIU
Mono-clonal anti-IgE antibody
Omalizumab
Omalizumab for Atopic Dermatitis

- 10 young adults with refractory AD (19-35 years)
- 300 mg SC q 2 weeks.
- SCORAD (SCORing Atopic Dermatitis) at 6 months
  - 2 excellent (reduction of >50%)
  - 5 satisfactory (reduction of 25-50%)
  - 3 patients poor (reduction <25%)

Anti-IgE(omalizumab)

- The Atopic Dermatitis Anti-IgE Paediatric Trial (ADAPT)
- A randomised, double-blind, placebo-controlled trial using the validated eczema score (SCORAD)
- 24 weeks in 62 children aged 4–19 years with severe AD given 300 mg SC q 2-4 wks.

Anti-IgE (omalizumab)

- 9 patients with severe AD average age 49 yrs.
- 50% good- excellent 12.5% moderate 37.5% no response
- 26 studies comprising 174 patients were reviewed
- A total of 129 patients (74.1%) beneficial response (little- exc)
- FLG mutation + may confer potential failure of treatment.

Hotze M, Increased efficacy of omalizumab in atopic dermatitis patients with wild-type filaggrin status and higher serum levels of phosphatidylcholines. Allergy. 2014 Jan;69(1):132-5.
Omalizumab for Atopic Dermatitis

- 7 children with refractory AD at CHU Sainte-Justine
- Mean age: 10.8 yrs (6 – 19)
- Comorbidities:
  - All had multiple food allergies, asthma, allergic rhinoconjunctivitis (RAST, epicutaneous tests +)
  - Multiple cutaneous infections

  Mean Equivalent Dose 0.0021 mg/kg/IU IgE
  (Max 375 mg SC q 2 wks) x 30 months

  Mean ScorAD: 75 reduced to 30 (3-6 months)
  High IgE <35,000 IUL reduced by 60%

Fig 2. Representation of the affected area of the atopic dermatitis and pictures of an affected limb and the face of patient 1, (A) before omalizumab and (B) after 12 months of treatment.
Fig 3. Representation of the affected area of the atopic dermatitis and pictures of the back and the legs of patient 7. (A) before omalizumab and (B) after 3 months of treatment.
Omalizumab for Atopic Dermatitis
Omalizumab for Atopic Dermatitis
Dupilumab for AD
human mAb targeting the IL-4 Ra subunit,

Efficacy and safety of dupilumab in adults with moderate-to-severe atopic dermatitis inadequately controlled by topical treatments: a randomised, placebo-controlled, dose-ranging phase 2b trial

Neil M. Graham, M.D., Thomas Bieber, M.D., Ph.D., M.D.R.A., Ross Rocklin, M.D., Jeffrey E. Ming, M.D., Ph.D., Haobo Ren, Ph.D., Richard Kao, Dr.P.H., Eric Simpson, M.D., Marius Ardeleanu, M.D., Steven P. Weinstein, M.D., Ph.D., Gianluca Pirozzi, M.D., Ph.D., Emma Guttmann-Yassky, M.D., Ph.D., Mayte Suárez-Fariñas, Ph.D., Melissa D. Hager, M.A., Neil Stahl, Ph.D., George D. Yancopoulos, M.D., Ph.D., and Allen R. Radin, M.D.

Lancet 2016; 387: 40–52
Dupilumab for AD

- March 2017, dupilumab received FDA approval
- A fully human monoclonal antibody that blocks interleukin-4 and interleukin-13, key drivers of Th2
- 3 arms to the study: Randomized, placebo-controlled or dupilumab at a dose of 300 mg SC q 2 week
  - ↓ pruritus, ↓ EASI score 50-75 significant
  - ↓ K16, a marker of keratinocyte proliferation
  - ↓ TARC, a key Th2 biomarker
- Injection-site reactions, conjunctivitis, nasopharyngitis and headache

Rituximab (a chimeric monoclonal anti-CD20 antibody)

- A small open trial of patients with severe AD who received 2 doses of 1000 mg by intravenous infusion for 2 weeks.
- Histology: ↓spongiosis, acanthosis, B cells in dermis (50%), & ↓ T-cell infiltrates
- ↓ IL-5 ↓ IL-13 ↓ total IgE but not allergen-specific IgE levels
- Minimal transient clinical improvement followed by deterioration.
- Combination of omalizumab and rituximab in patients effective
- Optimal therapy may require the use of several biologics

NEMOLIZUMAB

0.5 mg/kg SQ every 4 weeks improves pruritus, BSA
May develop edema

Other biologics in the future

**TRALOKINUMAB, LEBRIKIZUMAB**
- prevents IL-13 from binding to its receptor
- A phase 2b, RDPC trial finished in 2016 not yet reported

**USTEKINUMAB** the common p40 subunit of IL-12/IL-23.

JAK-Inhibitors

- Pruritus can be induced by ↑IL-31,11,12
- Suppressed by inhibition of the JAK-STAT pathway.
- JTE-052 rapid antipruritic effect from the night of study treatment initiation

JAK-Inhibitor oral

- Tofacitinib (I,3), moderate-to-severe AD SCORAD index decreased from 36.6 to 12.12 (66.6%; p < .05) from week 8-29
- Baricitinib (1,2)
- PF-04965842
- Upadacitinib (ABT-494).

Lessons Learned AD

1. Compliance?
2. Is it atopic dermatitis?
3. Allergen (pet, food, contact) infection, lymphoma
4. Systemic therapies: immunosuppressors, PDE4-inhibitors, biologics, JAK inhibitors