Asthma and its phenotypes

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Phenotypic evaluation of asthma

• Asthma heterogeneous disease
  ▪ Dx of asthma requires symptoms and reversible airway obstruction--many diseases meet
  ▪ Classification of phenotypes limited
  ▪ Previous classifications included allergic/extrinsic, non-allergic/intrinsic, aspirin sensitive, brittle

• Phenotype: “Characteristics of an organism resulting from the interaction of its genetic make-up and environment”

• Defining phenotypes should enhance understanding of pathobiology and ability to target therapy with biologics, etc
Potential breakdown of phenotypes

- Based on
  - Clinical aspects
  - Inflammation
  - Associated factors/triggers

- Can we begin to address overlap through integrated approaches to better target therapy?
I. Clinical Phenotypes

- Mild to severe
  - Easily controlled (mild) vs not easily controlled (severe)
- Not easily controlled/severe disease
  - Variable disease with frequent and/or severe exacerbations
  - Stable or progressive, but more marked airflow limitation
Severity

• Most broadly used classification of asthma
  ▪ but is severity truly a phenotype?
• “Severity” based on level of symptoms, FEV1 and medication needs to maintain “control”
  ▪ Very little longitudinal data suggest asthma progresses from mild to severe disease
    • Generally starts at some level of severity and stays there OR
    • “Second hit” moves patient from mild to more severe
• No specific biomarkers identified for each level
“Not severe” asthma

- Asthma that achieves arbitrary level of control on currently available medications
- Likely majority of asthmatics
- “May” be more likely to have onset in childhood and allergic component
Severe asthma: Easiest to identify phenotypes

- Asthmatics who do not achieve specified level of control despite gold standard therapy and adequate control of co-morbidities
- Two broad clinical categories
  - Exacerbating severe asthma
  - Progressive/stable but marked airflow limitation
  - Each meet ATS workshop criteria for severe asthma
  - May be subgroups of “severe disease” that either don’t have asthma at all, or have “more” than just asthma…i.e., bronchiectasis
Frequent/severe exacerbaters vs stable/progressive obstruction

- Exacerbations (frequent and/or severe) and obstruction recognized as two “risk domains”
- Don’t always occur in same subjects, but when do, likely contributes to even greater severity
- Associated with differences in:
  - Physiology
  - Pathology
  - Prognosis
  - Profound differences in AQLQ
Severe asthma patients have high HCU despite standard care

<table>
<thead>
<tr>
<th>Health Care Utilization</th>
<th>MILD</th>
<th>MODERATE</th>
<th>SEVERE</th>
</tr>
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<tbody>
<tr>
<td>ER Ever</td>
<td>58%</td>
<td>66%</td>
<td>86%</td>
</tr>
<tr>
<td>ER past year</td>
<td>10%</td>
<td>20%</td>
<td>43%</td>
</tr>
<tr>
<td>Hosp Ever</td>
<td>28%</td>
<td>33%</td>
<td>74%</td>
</tr>
<tr>
<td>Hosp past year</td>
<td>&lt;1%</td>
<td>6%</td>
<td>27%</td>
</tr>
<tr>
<td>ICU Ever</td>
<td>6%</td>
<td>9%</td>
<td>41%</td>
</tr>
<tr>
<td>Mechanical Vent</td>
<td>4%</td>
<td>6%</td>
<td>23%</td>
</tr>
</tbody>
</table>

In fact, over 75% of all severe (SARP) asthmatics have EITHER history of ICU stay (ever), ER visit/hospitalization OR more than 3 oral steroid bursts in previous year.
Severe exacerbaters more likely to:

• Be more reactive
  ▪ PC20 and BD responsiveness

• Have
  ▪ more sputum eosinophils
  ▪ more steroid side effects
  ▪ marginally lower FEV1
  ▪ definable triggers: sinus, GERD
  ▪ earlier age at onset

• Have no differences in:
  ▪ IgE or allergy skin testing

SARP, Unpublished
Anti-TNF-α in severe asthma: Clearly a need to phenotype

Proportion Free from Severe Exacerbations (n=309)

*P-value compares Combined 100mg & 200 mg vs. Placebo

- Placebo
- 50 mg q4 wks
- 100 mg q4 wks
- 200 mg q4 wks
- Combined 100 mg & 200 mg

p=0.08*
Reversibility: A key element of severe asthma exacerbating subset

<table>
<thead>
<tr>
<th></th>
<th>Reversibility &lt; 12% (n=144) Mean +/- SD</th>
<th>Reversibility ≥ 12% (n=164) Mean +/- SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline % predicted FEV₁</td>
<td>63.4 +/- 10.5</td>
<td>56.8 +/- 11.3</td>
</tr>
<tr>
<td>Baseline reversibility</td>
<td>5.5 +/- 5.0</td>
<td>26.1 +/- 14.2</td>
</tr>
</tbody>
</table>
Late onset, reversible with sinus hx much more likely to respond

Proportion Free from Severe Exacerbations (n=170)

P-value compares Combined 100mg & 200 mg vs. Placebo

Placebo
50 mg q4 wks
100 mg q4 wks
200 mg q4 wks
Combined 100 mg & 200 mg

Time (Week)
Percent Subjects
0 4 8 12 16 20 24
0 50 60 70 80 90 100

p<0.001
Genotypes also impact exacerbation “phenotype”

SNPs in IL-4Ralpha

- E375A
  - p=0.03

- Q551R
  - p=0.04

- Less frequent allele (in CA) associated with severe exacerbations
- Replicated in larger SARP cohort
- Significant with African Americans removed
- Similar differences in FEV1 by genotype

Declining FEV1 occurs in subset of asthma

- Previously published data (CAMP trial, NEJM 2002) did not suggest overall decline in FEV1 in any of 3 Rx groups
- However, subset analysis suggested decline in FEV1 in a subset, which was NOT impacted by treatment with ICS

Covar AJRCCM 2004
Being male and less allergic increased risk for decline in FEV1

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>FEV1 ↓</th>
<th>No ↓ FEV1</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>7.6±2</td>
<td>8.4±2</td>
<td>0.0001</td>
</tr>
<tr>
<td>Male sex</td>
<td>70%</td>
<td>57%</td>
<td>0.0003</td>
</tr>
<tr>
<td>Age at dx</td>
<td>3.4±2</td>
<td>4.1±3</td>
<td>0.0004</td>
</tr>
<tr>
<td>Atopy</td>
<td>77%</td>
<td>87%</td>
<td>0.0004</td>
</tr>
<tr>
<td>Serum IgE</td>
<td>928</td>
<td>1281</td>
<td>0.05</td>
</tr>
</tbody>
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II. Inflammatory Phenotypes

- Eosinophilic
  - More common exacerbating phenotype
  - Strong evidence links symptoms, exacerbations and response to therapy
  - Less relation to atopy
- Non-eosinophilic
  - More likely to be obese
  - Relationship to smoking
  - May exacerbate less due to *asthma* and more due to co-morbidities
  - Neutrophilic inflammation may relate to lower FEV1
Eosinophilic inflammation: The ultimate exacerbation (death)
Persistent eosinophils: greater symptoms/severe exacerbations

*Symptoms “most or all of the time”

Miranda, JACI, 2004
Controlling eosinophilic inflammation decreases exacerbations

- Asthma managed by current British Thoracic Society guidelines vs #s of sputum eosinophils
- Increased eosinophils “predict” exacerbation-related disease
- Low eosinophils in sputum predict few exacerbations and lower ICS dose

*Green. Lancet 2002*
$\text{FeNO}$ increased with eosinophilic inflammation

Neutrophilic asthma: General increase with severity

Jatakanon, et al.
Am J Respir Crit Care Med 1999
Neutrophilic inflammation poorly responsive to CSs

- Abundant neutrophils in sputum may limit response to CS
- Increased in smoking asthmatics
  - Green, Thorax 2002
III. Asthma Triggers: Allergic asthma/early onset disease

Hx eczema (p<0.001)
Early 40%  Late  4%

Higher serum IgE
Family hx of asthma
  Early>late
More lymphocytic
  Th2? inflammation

Miranda, J Allergy Clin Immunol Jan 2004
Mold allergy: Predicts more severe disease

<table>
<thead>
<tr>
<th>Allergen</th>
<th>Asthma, no admission (n=82)</th>
<th>Asthma, 2+ admission (n=46)</th>
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</thead>
<tbody>
<tr>
<td>Aspergillus</td>
<td>7 %</td>
<td>37 %</td>
</tr>
<tr>
<td>Alternaria</td>
<td>5 %</td>
<td>26 %</td>
</tr>
<tr>
<td>Cladosporium</td>
<td>1 %</td>
<td>41 %</td>
</tr>
<tr>
<td>Penicillium</td>
<td>2 %</td>
<td>30 %</td>
</tr>
<tr>
<td>Candida</td>
<td>10 %</td>
<td>33 %</td>
</tr>
<tr>
<td>Any fungal allergen</td>
<td>16%</td>
<td>76%</td>
</tr>
</tbody>
</table>

O’Driscoll et al, BMC Pulmonary Medicine 2005;5:4
Role of Chitinases: “Very trendy”...

While AMCase has chitinase activity, YKL-40, and most others in humans, do not. Therefore, link between fungal/insect allergens, still unclear.

Allergic asthma may respond better to anti-IgE Rx

No. of hospitalizations due to serious asthma exacerbation

Pooled analysis from studies 008 and 009

Study 010

28 weeks core period

52 weeks core + extension

28 weeks core period

Th2 intervention improves allergic responses in mild asthma

*Pitrikinra* is a 14 kDa IL-4 mutein that inhibits assembly of IL2Rγ or IL13Rα into receptor complexes with IL-4Rα.
Pitrikinra decreases allergen induced exacerbation

3.7-fold reduction in average LAR FEV$_1$ %fall from pre-challenge baseline

95% CI on ratio of ANCOVA-adjusted means, placebo / AEROVANT = (2.1, 6.3)

$p < 0.001$

Mean ± SEM (n = 14 placebo, 15 AEROVANT)

Wenzel, Lancet, October 2007
Inhibition of IL-4Rα pathway improves allergic inflammation

- Blocking IL-4Ralpha decreased FeNO at baseline and tended to decrease FeNO after allergen challenge
- Studies in atopic derm showed effect on IgE as well
- Same IL-4R genotypes identified with risk/inflammation may respond best to Rx

Wenzel, the Lancet Oct 2007
IL-4Rα genotypes also associate with increased mast cells

C allele for E375A associated with greater # and % of IgE (+) cells in airways

High IgE (+) mast cells in airways risk factor for high intensity exacerbations

Balzar JACI 2007
Late onset: “Aspirin sensitive-like”

- Adult onset eosinophilic asthma
- May or may not have hx of exacerbation in response to NSAID
- Often with sinusitis, sometimes bronchiectasis
  - Some patients appear to respond to anti-fungal Rx but don’t meet criteria for ABPA
- Association with occupational exposure?
- Highly eosinophilic (more so than allergic/early onset)  Miranda 2004/SARP
- Rx implications: LTRA/5 LO inhibitor…maybe anti-TNF-alpha and maybe anti-fungals
Eosinophils in tissue more common in late onset disease

Likely reflection of more aspirin sensitive-like asthma

Late onset disease: higher urinary LTE4 levels \( p=0.009 \)

Sputum eos higher in late onset asthma: SARP

Miranda JACI 2004
Randomised trial of itraconazole in ABPA - results

Corticosteroid dependant ABPA with asthma
Phase 1 - 200mg BID v placebo, 16 weeks
Phase II - 200mg daily in all patients, 16 weeks

<table>
<thead>
<tr>
<th></th>
<th>Itra</th>
<th>Placebo then Itra</th>
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<tbody>
<tr>
<td><strong>Phase 1</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall response</td>
<td>13/28 (46%)</td>
<td>5/27 (19%) p=0.04</td>
</tr>
<tr>
<td><strong>Phase 2</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No prior response (n=33)</td>
<td>4/13 (31%)</td>
<td>8/20 (40%) NS</td>
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Others

• Premenstrual/hormonal
  ▪ Role of genetic factors
    • Severe female asthmatics: lower PGE2/15 PGDH levels
  ▪ Role for hormonal manipulation?

• Distal lung inflammation
  ▪ Fine particle aerosols/systemic anti-inflammatories

• Obesity
  ▪ Strong association with GERD
  ▪ Non-eosinophilic/non-Th2 asthma may respond to weight loss strategies

• Smoking
  ▪ Smoking cessation
Late onset/
ASA-like/occupational
Fungal?

Eosinophilic/?Th2-biased

Allergic/early onset

Hormonal/
PMA

Exacerbating:
Eosinophilic/steroid responsive
Exacerbating: Less steroid responsive

- Obese/GERD
- Smokers
- Noneosinophilic
Progressive/stable airflow limitation

- Post-infectious/other bronchiolitis
- Smoking or past smoking asthma
- Remodeled/burned out disease (Well treated?)
However...

- Those with FEV1 decline had no more or less use of steroids
- Had LESS health care utilization (hospitalizations) than those without decline in FEV1
- Had no difference in PC20 compared to those that did not decline
Eosinophils not found in all asthma tissues

Wenzel et al., Am J Respir Crit Care Med 1999;160:1001-08.
In vivo, iNOS protein highly correlated with Fe$_{NO}$

Spearman’s $\rho = 0.92$
$p = 0.0002$

iNOS protein increases with severity, while FeNO does not