Phenotyping Asthma: Environmental and Occupational Asthma

Nicholas Kenyon, MD, MAS

Pulmonary, Critical Care, Sleep Medicine
UC Davis Asthma Network

EHS CENTER
UC Davis Environmental Health Sciences Center

Disclosures:

Clinical Trial Contract: Genentech

Consulting: Astra Zeneca May, 2017 for FDA submission

Other Research support: NIH (NHLBI, NIAID, NCATS, NIEHS, NIBIB) CA Air Resources Board, Hartwell foundation
Summary: Phenotyping Asthma and Occupational Asthma

- Epidemiology and Trends for Asthma and Occupational Asthma
- Phenotyping and Biologics for Asthma
  - Anti-IgE, Anti-IL5, Anti-IL13, Anti-IL4/IL13
- Evaluation and Phenotyping for Occupational Asthma

Cal Fire Chief

58 yo Cal Fire Chief with history of mild asthma suffered marked worsening of his asthma after 6 week exposure to wildfires two years ago. Now on high dose ICS, long acting beta agonists, tiotropium, prednisone. Placed on disability and interested in returning to work.

PE: Healthy appearing, decreased expiratory flow.
Lung function: FEV1 55% predicted
Exhaled Nitric Oxide 12 ppb
IgE 20, RAST neg.
Eosinophil count 100/mm3

What is best treatment approach for this patient?
Teacher, Washoe County

50 yo former teacher moved to departmental offices in basement of old building. Over 12 months, he noted increasing dyspnea while at work and exposed to moist “moldy” environment. Symptoms improved while away from work for several days and vacation. Placed on disability temporarily and in negotiations.

PE: Anxious, nasal turbinates swollen, no wheezing
Lung function: FEV1 = 75% predicted
Exhaled Nitric Oxide 120 ppb
IgE 20o, RAST + grasses, molds, trees
Eosinophil count 1=500/mm3

What is best treatment approach for this patient?

Asthma Prevalence in the World, 2008

Anandan et al. Allergy 2010
Factors Associated with Asthma Hospitalizations, California
California Department of Public Health, 2010

Ethnicity and Asthma Hospitalizations, CA
Epidemiology of Asthma in the workplace:
15% of 30,000,000 adult asthmatics, US

- Biases:
  - Studies are occupation and employee based
  - Most cohort studies of cleaning product asthma are in women.
  - Ethnic differences are less striking than the general population.

What are the structural airway changes in adults with asthma?
Phenotyping in Asthma

- Allergic vs Irritant-induced/non-allergic
- Adult onset asthma (e.g. Occupational asthma)
- High/Low Th2 (“T2”) asthma
  - High/low Exhaled Nitric Oxide (FeNO)
  - High/Low Periostin
- Neutrophilic vs Eosinophilic Asthma
- Steroid resistant
- Aspirin exacerbated Respiratory Disease
- ACOS—asthma/COPD overlap syndrome
Not all asthmatics respond the same to steroids.
Th2 High vs. Th2 Low Phenotype
Woodruff et al. AJRCCM 2009

Asthma gene polymorphisms of the $\beta_2$-adrenergic receptor

<table>
<thead>
<tr>
<th>Population Genotype</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>16% Arg/Arg</td>
<td></td>
</tr>
<tr>
<td>37% Arg/Gly</td>
<td></td>
</tr>
<tr>
<td>47% Gly/Gly</td>
<td></td>
</tr>
<tr>
<td>African Americans</td>
<td></td>
</tr>
<tr>
<td>30% Arg/Arg</td>
<td></td>
</tr>
</tbody>
</table>

FDA is mandating safety study with 50,000 patient lives

McGraw et al., JCI 1998
Albuterol response by genotype (BARGE)

331 asthmatics
mild asthma
18-55 yrs age

55 Arg/Arg
37 randomized
17 albuterol
16 completed

125 Gly/Gly
41 randomized
20 albuterol
17 completed

21 placebo
17 completed


Response to β-agonists/Anticholinergics by genotype

β-agonists

Anticholinergics

February 22, 2018 / WOEMA 2018 Webinar Series
Anti-IgE (Omalizumab, Xolair): Humanized monoclonal anti-IgE antibody

Omalizumab: Analysis of Biomarkers, 10 yrs experience
Hanania et al AJRCCM 2013
(Exhaled NO, Eosinophils, Periostin)

Exacerbation rates

<table>
<thead>
<tr>
<th></th>
<th>Low FeNO at baseline</th>
<th>High FeNO at baseline</th>
<th>Low eosinophils at baseline</th>
<th>High eosinophils at baseline</th>
<th>Low periostin at baseline</th>
<th>High periostin at baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Omalizumab</td>
<td>0.73</td>
<td>0.66</td>
<td>1.03</td>
<td>0.72</td>
<td>0.72</td>
<td>0.66</td>
</tr>
<tr>
<td>Placebo</td>
<td>0.71</td>
<td>1.07</td>
<td>0.72</td>
<td>1.03</td>
<td>0.72</td>
<td>0.93</td>
</tr>
</tbody>
</table>
Cytokines and Effector Cells of Interest in Asthma

**Effector Cells**
- Eosinophil
- Mast cell
- Th2 cell
- Dendritic cell

**Key Cytokines**
- IL-4
- IL-5
- IL-13
- IL-17


---

**Effects of humanized monoclonal Ab on blood/sputum eosinophils, airway hyper-responsiveness, late asthmatic response.**


- 24 mild asthmatic subjects given single dose of anti IL5 antibody or placebo
- 3 inhaled allergen challenges were performed to assess EAR and LAR
- Primary endpoint was blood and sputum eosinophil counts after allergen challenge
- No effect on asthma response

---
Mepolizumab in severe eosinophilic asthma (DREAM)
Pavord et al. Lancet 2012

- 81 center RCT, 1:1:1:1 randomization
- Severe asthma with 2 oral steroid bursts/yr
- Sputum eos >3% or FeNO > 50 ppb or blood eos >300/ml
- Primary outcome: oral steroid bursts, ED visit, hospital

IV vs Subcutaneous Mepolizumab, Asthma Exacerbations and FEV₁

- Multicenter, RCT with 576 asthmatics with high eosinophil counts and recurrent asthma exacerbations despite high dose ICS + LABA, and FEV₁ < 80% predicted
- Randomized to 100 mg sq, 75 mg IV, or placebo monthly
- RESULT: The rate of exacerbations was reduced by 47% among patients receiving intravenous mepolizumab and by 53% among those receiving subcutaneous mepolizumab, as compared with those receiving placebo
IL-4 and IL-13 signaling in allergic airway disease

Naina Gour, Marsha Wills-Karp
Cytokine 2015

Gour and Wills-Karp

IL-4 and IL-13 signaling in allergic airway disease

Naina Gour, Marsha Wills-Karp

Cytokine 2015

Gour and Wills-Karp

IL-13

Epithelial cells

TGFβ

Monocytes

Myeloid cells

IL-4

IL-13

Goblet cell hyperplasia

MUC5AC

AR

Perilipin

BRP-39

AAM

Polyamines

Proline

Fibroblasts

Collagen

ECM

KEY

Contractile receptor agonist

β-adreno-receptor

MLC phosphatase

MLC kinase

Contractions

Airway Smooth Muscle

CONTRACTION

Actin-Mysin cross-bridging

Calcium

CD38

NADPH

Ca2+

ROCK

Rho-kinase

RhoGTPase

IL-4 and IL-13Rα1: Primary and Secondary End Points

A. Exacerbations — Primary End Point

B. Time to Exacerbation

C. FEV₁

D. Nocturnal Asthma


Dupilumab (IL-4Rα/ IL-13Rα1): Primary and Secondary End Points
### Target Drug Mechanism of action Status

<table>
<thead>
<tr>
<th>Target</th>
<th>Drug</th>
<th>Mechanism of action</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-5</td>
<td>Mepolizumab SB-240563</td>
<td>Block IL-5</td>
<td>Submitted to the FDA for asthma in November 2014. Ongoing trials in asthma, COPD, HES, EoE, EGPA, nasal polyps, and eosinophilic cystitis.</td>
</tr>
<tr>
<td></td>
<td>Reslizumab SCH55700</td>
<td></td>
<td>Phase 3 trials in asthma and EoE completed and open-label extension ongoing.</td>
</tr>
<tr>
<td>IL-5Ra</td>
<td>Benralizumab MEDI-563</td>
<td>Inhibits IL-5 binding to receptor</td>
<td>Ongoing trials in asthma, COPD, and HES.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Depletes eosinophils through enhanced ADCC</td>
<td></td>
</tr>
<tr>
<td>CCL-11</td>
<td>Bertilimumab</td>
<td>Block CCL-11</td>
<td>Not yet recruiting in ulcerative colitis and bullous pemphigoid, planned in asthma.</td>
</tr>
<tr>
<td></td>
<td>Siglec-8</td>
<td></td>
<td>In preclinical development.</td>
</tr>
<tr>
<td>IgE</td>
<td>Omalizumab Xolair</td>
<td>Block IgE</td>
<td>Ongoing trials in mastocytosis, chronic urticaria, asthma, AERD, nasal polyposis, EoE, eosinophilic gastroenteritis, and hyper-IgE syndrome.</td>
</tr>
<tr>
<td>IL-4R/ IL-13Rα</td>
<td>Dupilumab REGN668 AMG 317</td>
<td>Inhibit binding of IL-4 and/or IL-13 to IL-4Rα</td>
<td>Ongoing trials in asthma, nasal polyposis, atopic dermatitis, and ulcerative colitis. Ongoing trials in asthma.</td>
</tr>
<tr>
<td></td>
<td>Lebrikizumab ILR1444A Tralokinumab Annukinzumab</td>
<td>Block IL-13</td>
<td>Ongoing trials in asthma and idiopathic pulmonary fibrosis. Ongoing trials in asthma, ulcerative colitis, and idiopathic pulmonary fibrosis.</td>
</tr>
<tr>
<td>IL-4/IL-13</td>
<td>QBX258 VAA694 +QAX576 SAR156597 Bispecific antibody</td>
<td>Block both IL-4 and IL-13</td>
<td>Ongoing trials in asthma. Ongoing trial in idiopathic pulmonary fibrosis.</td>
</tr>
<tr>
<td>TSLP</td>
<td>AMG 157 MEDI9929</td>
<td>Block TSLP</td>
<td>Ongoing trials in asthma and atopic dermatitis.</td>
</tr>
<tr>
<td>IL-17Ra</td>
<td>Brodalumab</td>
<td>Inhibits IL-17A, IL-17F, and IL-25 binding to receptor</td>
<td>Ongoing trials in asthma and psoriasis.</td>
</tr>
</tbody>
</table>

---

### University of California Asthma Network (UCAN) Bronchial Thermoplasty Program

- The first Bronchial Thermoplasty Program in the Western United States.
- All patients will undergo a comprehensive clinical, diagnostic and therapeutic asthma evaluation in the UCAN clinic.
- Appropriate patients will undergo bronchial thermoplasty only after careful screening and evaluation.
- Close follow-up and management in the UCAN clinic.
The Demographics of UBIOPRED Severe Asthma cohort

<table>
<thead>
<tr>
<th></th>
<th>Severe asthma: non-smoking (308)</th>
<th>ACOS (110)</th>
<th>Moderate Asthma (98)</th>
<th>Non-asthma (101)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>50.9</td>
<td>54.5</td>
<td>42.4</td>
<td>38.9</td>
</tr>
<tr>
<td>Female (%)</td>
<td>65.91</td>
<td>50.91</td>
<td>50.00</td>
<td>38.61</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>29.08</td>
<td>29.56</td>
<td>25.88</td>
<td>25.31</td>
</tr>
<tr>
<td>Exacerbations/yr</td>
<td>2.48</td>
<td>2.55</td>
<td>0.37</td>
<td>0</td>
</tr>
<tr>
<td>IgE (IU/ml)</td>
<td>119.5</td>
<td>126</td>
<td>89.4</td>
<td>23.45</td>
</tr>
<tr>
<td>Atopy (%)</td>
<td>69</td>
<td>58</td>
<td>80</td>
<td>38</td>
</tr>
<tr>
<td>Nasal polyps (%)</td>
<td>34.7</td>
<td>33.7</td>
<td>8.3</td>
<td>8.8</td>
</tr>
<tr>
<td>FEV₁ (% pred)</td>
<td>67.42</td>
<td>67.25</td>
<td>88.37</td>
<td>101.76</td>
</tr>
<tr>
<td>Oral corticosteroids (%)</td>
<td>50.68</td>
<td>46.08</td>
<td>1.06</td>
<td>0</td>
</tr>
<tr>
<td>Sputum eosinophils (%)</td>
<td>2.75</td>
<td>4.13</td>
<td>1.05</td>
<td>0.00</td>
</tr>
<tr>
<td>Exhaled NO</td>
<td>27</td>
<td>23.5</td>
<td>25.50</td>
<td>19.00</td>
</tr>
</tbody>
</table>

UC Davis Asthma Network (UCAN) clinics (1999-2014)
850+ patients—74% Female, mean age 46.3±15.3
58.6% Severe persistent, 33.9% Moderate persistent

UC Davis Asthma Network Clinic
Three pulmonary asthma specialists
Two full time respiratory therapists
“UCAN Quit” smoking cessation clinic
Biologics clinic
Bronchial Thermoplasty clinic
Algorithm for Work Associated Asthma
Dumas et al Curr All Clinical Immunol 2016

Standards in the Diagnosis of Occupational Asthma

- A worker receives a diagnosis of de novo asthma, or recrudescence of previously quiescent asthma
- A worker is exposed to a sensitizing agent or an irritant in the workplace that is known to cause occupational asthma.
- A sufficient causal relationship is established between the causative agent and the worker’s symptoms.
### TABLE I. Selected Causes of Occupational Asthma

<table>
<thead>
<tr>
<th>High Molecular Weight Compounds</th>
<th>ANAGENTS</th>
<th>OCCUPATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANIMAL PRODUCTS: Fat, Excreta, Serum, Secretions</td>
<td>Animal handlers</td>
<td>Laboratory workers</td>
</tr>
<tr>
<td>PLANTS: Grain, Tea, Flour, Tobacco, Moss</td>
<td>Grain handlers</td>
<td>Textile workers</td>
</tr>
<tr>
<td>ENZYMES: B. subtilis, Pancreatic extracts, Papain, Trypsin, Fungal amylase</td>
<td>Bakers</td>
<td>Food processing workers</td>
</tr>
<tr>
<td>VEGETABLE: Gum acacia, Gum tragacanth</td>
<td>Printers</td>
<td>Paper industry workers</td>
</tr>
<tr>
<td>OTHER: Crab, Prawn</td>
<td>Crab and shrimp processors</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Low Molecular Weight Compounds</th>
<th>AGENTS</th>
<th>OCCUPATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>DISOCYANATES: Toluene diisocyanate (TDI) workers, Methylenediphenyl diisocyanate (MDI)</td>
<td>Polyurethane industry workers</td>
<td>Plastic industry workers</td>
</tr>
<tr>
<td>Painters' allergens</td>
<td>Workers using varnish</td>
<td>Forestry workers</td>
</tr>
</tbody>
</table>

| Other Organic CHEMICALS | Urea, formaldehyde, Dyes, Formic acid, Acetylsalicylic acid, Hexachlorocyclohexane, Dimethyl, Ethanolamine, Polyvinyl chloride, Polyethylene, Polypropylene | Other industries |

*Mechanisms believed to be IgE-mediated for high molecular weight compounds and for some low molecular weight compounds. The immunological mechanism for some low molecular weight substances remains undefined. (Adapted from M. Chan-Yeung, S. Lam, Occupational Asthma, Ann Rev Respir Dis 1994; 157:666-703.)

### Incidence of occupational asthmas in main occupational groups according to cross-sectional studies.

#### Allergology International 2017

<table>
<thead>
<tr>
<th>Occupation/exposed antigen</th>
<th>Number of cases</th>
<th>Incidence (%)</th>
<th>Country</th>
</tr>
</thead>
<tbody>
<tr>
<td>Snow crab processors</td>
<td>303</td>
<td>15.6</td>
<td>Canada</td>
</tr>
<tr>
<td>Guar gum (natural polysaccharide)</td>
<td>151</td>
<td>3.0</td>
<td>Canada</td>
</tr>
<tr>
<td>Painters (isocyanate)</td>
<td>730</td>
<td>7.1 (All subjects were non-smokers.)</td>
<td>Italy</td>
</tr>
<tr>
<td>Poultry workers</td>
<td>134</td>
<td>11.0</td>
<td>South Africa</td>
</tr>
<tr>
<td>Rats allergens</td>
<td>113</td>
<td>4.4</td>
<td>France</td>
</tr>
<tr>
<td>Natural rubber latex (health care workers in general hospital)</td>
<td>196</td>
<td>7.1</td>
<td>Italy</td>
</tr>
<tr>
<td>Florists</td>
<td>128</td>
<td>14.1</td>
<td>USA</td>
</tr>
<tr>
<td>Supermarket bakery workers</td>
<td>66</td>
<td>9.0</td>
<td>UK</td>
</tr>
<tr>
<td>Strawberry growing industry workers</td>
<td>43</td>
<td>4.7</td>
<td>Japan</td>
</tr>
<tr>
<td>Oyster shucker (Sea squirt)</td>
<td>250–417</td>
<td>18.0–36.0</td>
<td>Japan</td>
</tr>
</tbody>
</table>
Phenotyping Asthma: Environmental and Occupational Asthma / Nicholas Kenyon, MD, MAS

February 22, 2018 / WOEMA 2018 Webinar Series

---

Does this patient have a type of work related asthma?

Q1: Does the patient have asthma?
Q2: Are symptoms worse at work?

No → Preliminary Diagnosis: Work Related Asthma

Yes →

Q3: Is Primary Criteria A true?

Yes → Work Aggravated Asthma

No → New onset asthma

Primary Criteria

A. Worsening asthma in presence of pre-existing asthma
B. New asthma that develops within 24 hrs of massive exposure
C. Exposure at workplace to a compound known to cause OA
D. Decrease in PEFR/FEV1 at workplace
E. Documented worsening of bronchial hyperresponsiveness to methacholine during work
F. Bronchial hyperresponsiveness after exposure to specific inhaled workplace irritant (SIC)

4) Is Criteria B true?

No → Occupational Asthma

5) Is Criteria C true?

No →

6) If Yes, is either D, E, or F true?

No → Occupational Asthma with unknown inducer and no objective evidence

Yes → Occupational Asthma with known inducer and objective evidence

---

Traditional Testing for Occupational Asthma

<table>
<thead>
<tr>
<th>Test</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Questionnaire</td>
<td>Yes</td>
<td>No</td>
<td>Simple</td>
</tr>
<tr>
<td>MCh Challenge</td>
<td>Yes</td>
<td>No</td>
<td>Test for asthma, not OA</td>
</tr>
<tr>
<td>Spirometry before and after work</td>
<td>No</td>
<td>No</td>
<td>Simple</td>
</tr>
<tr>
<td>PEFR monitoring</td>
<td>+/-</td>
<td>No</td>
<td>Patient cooperation needed</td>
</tr>
<tr>
<td>Immunologic testing</td>
<td>Yes</td>
<td>+/-</td>
<td>HMW and some LMW compounds (IgE response needed)</td>
</tr>
<tr>
<td>Specific Inhalation challenge</td>
<td>Yes</td>
<td>Yes</td>
<td>Where?</td>
</tr>
</tbody>
</table>

---
Future of Phenotyping: Breath analysis in the 2000’s

- AHRQ 2017 Statement on Exhaled Nitric Oxide
  - FeNO > 44 ppb has a positive predictive value for the diagnosis of asthma of 94%

What if you exhaled diagnostic information on a continual basis ???

- Odors and metabolites in human breath are important
- Volatile and non-volatile compounds exhaled
- Sampling and analysis are HUGE issues…
Breath Biomarker Exposome in Jet Fuel Workers
Pleil et al 2011, J Breath Research

<table>
<thead>
<tr>
<th>Compounds</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzene</td>
</tr>
<tr>
<td>Ethylbenzene</td>
</tr>
<tr>
<td>1,3,5-trimethylbenzene</td>
</tr>
<tr>
<td>o-xylene</td>
</tr>
<tr>
<td>Toluene</td>
</tr>
<tr>
<td>Dodecane</td>
</tr>
<tr>
<td>Undecane</td>
</tr>
<tr>
<td>Decane</td>
</tr>
<tr>
<td>Nonane</td>
</tr>
</tbody>
</table>

Diagnostic utility of exhaled breath condensate analysis in suspected work-related asthma.

OA – Occupational asthma
WEA – Work exacerbated asthma
WRA – Work related asthma
NWRA – Non-work related asthma

P = .0047
Can this be done with Exhaled Breath Condensate (EBC)?

Ko F. et al. Are exhaled breath condensate useful in monitoring asthma? Current Allergy and Asthma Reports 2007, 7:65

1st Generation Prototype for Combined Spirometer and Breath Sensor

- The user starts the application
- Tidal breathing is performed for 15 seconds
- User then fully inhales and exhales for 6 seconds
- Peak expiratory flow (PEF), spirometry graph, Forced expiratory volume 1 (FEV1), FEV6 is displayed
- Data is stored and transferred electronically.
Breath biomarker phenotyping will be a reality in our careers.

Cal Fire Chief

58 yo Cal Fire Chief
Lung function: FEV1 55% predicted
Exhaled Nitric Oxide 12 ppb
IgE 20, RAST neg.
Eosinophil count 100/mm3

What is best treatment approach for this patient?

Pt was treated with bronchial thermoplasty x 3. No change in lung function but marked improvement in asthma symptoms. Discontinued prednisone. Trying to get back into department.
Teacher, Washoe County

50 yo former teacher exposed to moist “moldy” environment.
Lung function: FEV1 = 75% predicted
Exhaled Nitric Oxide 120 ppb
IgE 20o, RAST + grasses, molds, trees
Eosinophil count 1=500/mm3

What is best treatment approach for this patient?
Given high eos count, patient started on mepolizumab with improvement in asthma flares and allergic symptoms. Has not returned to work and diagnosed with OA, non-sensitizer.

Summary and Acknowledgements

1. Phenotyping patient with difficult to control asthma is becoming clinically relevant.
2. New biologic therapies will become the norm in severe asthma.
3. Tools for biomarker development in asthma are available.
4. Care of patients for severe asthma will benefit over the next 10 years.
5. Handouts/Publications: