Adult asthma diagnosis and treatment

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WHO definition of severe asthma (tentative, paper in process of approval)

- Diagnosis of asthma
- Control
- Future risks
- Treatment based on guidelines
- Availability and affordability of treatments
- Quality of treatments

"Uncontrolled asthma which can result in risk of frequent severe exacerbations (or death) and/or adverse reactions to medications and/or chronic morbidity (including impaired lung function or reduced lung growth in children)."

"Severe asthma"

Global Initiative for Asthma (GINA) 2005 guidelines include anti-IgE therapy at step 4

Outcome: asthma control
Outcome: best possible results

Comparison of ICS, LTRA and Placebo in asthmatic patients (≥15 Years) not controlled on prn β2-Agonists

Beclomethasone (n=246)
Montelukast (n=375)

Distribution of individual asthmatic patient responses to the 2 active treatments

Mepolizumab for Prednisone-Dependent Asthma with Sputum Eosinophilia

- Highly efficacious in other eosinophilic disorders (e.g., some but not all) hyper eosinophilic syndromes

- Mepolizumab
  - Placebo

- Treatment: Placebo vs 250 mg, 750 mg

Mepolizumab for severe eosinophilic asthma (DREAM): a multicentre, double-blind, placebo-controlled trial.

- 621 asthmatic patients with a history of recurrent severe asthma exacerbations, and ongoing eosinophil inflammation randomised iv mepolizumab (75 mg, 250 mg, or 750 mg) or placebo; 13 infusions at 4-week intervals.

- Primary outcome: rate of clinically significant asthma exacerbations requiring oral corticosteroids, admission, or a visit to an emergency department.

- Rate of clinically significant exacerbations was 2.40 per patient per year in the placebo group, 1.24 in 75 mg group (48% reduction), 1.46 in the 250 mg group (59% reduction) and 1.15 in the 750 mg group (52% reduction).

Mepolizumab is an effective and well tolerated treatment that reduces the risk of asthma exacerbations in patients with severe eosinophilic asthma.

Secondary outcome measures: Change in blood eosinophil counts pre-bronchodilator FEV1, ACQ and AQOL

- Number of exacerbations in each treatment group

- Cumulative number

- Frequency

- Blood eosinophils

- ACQ

- FEV1
Targeting the IL-5 Receptor α to ablate the Th2 response with an Antibody-Dependant Cell Cytotoxic (ADCC) antibody, MEDI-563

Therapeutic antibody and ADCC

Safety profile, pharmacokinetics, and biological activity of MEDI-563, an anti-IL-5 receptor alpha antibody, in a phase I study of subjects with mild asthma.


Multifunctional actions of IL-13

Increased sputum and bronchial biopsy IL-13 expression in severe asthma.

Safety profile, pharmacokinetics, and biological activity of MEDI-563, an anti-IL-5 receptor alpha antibody, in a phase I study of subjects with mild asthma.


Biotherapeutics: targeting IL-13 and IL-4: a massive investment by industry

IL-4 and IL-13 receptor complex: a major therapeutic target in asthma

IL-4 and IL-13 receptor complex: a major therapeutic target in asthma

Mean decrease in serum IgE at 12 weeks with highest dose of AMG 317 from 556 to 282 IU/mL

Biotherapeutics: targeting IL-13 and IL-4: a massive investment by industry

AMG 317 (AMGEN)

AMA-636 (Wyeth)

TNK550 (Genentech)

E-139 (Merck & Novartis)/IL-13Ra1

DOM1000P

DOM0910

UCB

Candidate

Nurvanca (immunex)

Pitrakinra (Aerovance)

AMG 317 (AMGEN)

CAT-354 (Medimmune)

IMA-636 (Wyeth)

TNK550 (Genentech)

E-139 (Merck & Novartis)/IL-13Ra1

DOM1000P

DOM0910

UCB

Specificity

sIL-4R

IL-4Ra

IL-4Ra

IL-13

IL-13

IL-13

IL-13

IL-13

IL-4L/IL-13

IL-4L/IL-13

IL-4L/IL-13

Format

Discontinued

Preclinical I II III

IL-4

IL-4Rα

IL-4Ra

IL-13

IL-13

IL-13

IL-13

IL-13

IL-4Rα

IL-4L/IL-13

Pubmed: IL-13 publications up to 2010

All entries: 2968

Allergy: 1000

Asthma: 142

Animal/asthma: 417

Mouse/asthma: 347

Human: 66 (reviews 52)

Human sputum or biopsy: 6 (2 reviews)

Original research:

Inflammatory biomarkers in airways of patients with severe asthma compared with non-severe asthma.

McAuley P, Hew M, Torrego A, Jouneau S, Davis T, Durham A, Chung KF.


Immuno-regulatory cytokines in asthma: IL-13 and IL-4 in induced sputum.


Clin Exp Allergy. 2001 Sep;31(9):1441-8

Increased sputum and bronchial biopsy IL-13 expression in severe asthma.


Increased sputum and bronchial submucosal IL-13 expression in asthma and eosinophilic bronchitis.


Increased sputum and bronchial biopsy IL-13 expression in severe asthma.

McAuley P, Hew M, Torrego A, Jouneau S, Davis T, Durham A, Chung KF.


Increased sputum and bronchial biopsy IL-13 expression in severe asthma.

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**Up-Regulation of IL-13 in human asthma**

- Saha SK et al. Increased sputum & bronchial biopsy IL-13 expression in severe asthma. J Allergy Clin Immunol 2008;121:685-91

**Th2-driven inflammation defines major subphenotypes of asthma**


**IL-13 inducible epithelial genes in airway epithelium**

- Periostin
- CLCA1
- Serpin B2

**Clinical features of asthma are present in patients with Th2-high and Th2-low asthma**

**Therapeutic targets in the allergic cascade that have so far failed to meet expectations in asthma clinical trials**

- **Mediators:** histamine, prostaglandins (D2, F2a, TxA2), non-cysteinyl LTs (LTB4), tryptase, PAF, bradykinin, neuropeptides.
- **Cytokines:** IL-4, -5, -9, 13, TNFα.
- **Chemokines:** CCL3, eotaxin.
- **Adhesion molecules:** α4 (VCAM), ICAM-1, E selectin, P selectin.
- **Receptors:** CD4, CD23 (low affinity IgE receptor), CD25 (IL-2 receptor).

**Stratified Medicine: What are we talking about?**

"the tailoring of medical treatment to the individual characteristics of each patient ... involves the use of companion diagnostics to achieve the best outcomes in the management of a patient’s disease or disease predisposition. Preventive or therapeutic interventions can then be concentrated on those who will benefit, sparing expense and side effects for those who will not".

Adapted from: "Priorities for Personalized Medicine" by the US President’s Council of Advisors on Science and Technology (PCAST), 2008

- Personalised Medicine has arrived to an extent:
  - Herceptin®, Gleevec®, Selzentry™, Ziagen®, Vectibix®, Iressa™
**Toward Precision Medicine**

Building a Knowledge Network for Biomedical Research and New System of Health

Medicine will move from a reactive to a proactive discipline over the next decade; one that is predictive, personalised, preventive and participatory.

The promise of personalised medicine

- More effective medicines
- Safer medicines
- Cheaper medicines
- Better healthcare
- Cheaper healthcare
- Less (rather than more) healthcare disparity

**SARP Clinical Cluster Analysis**

<table>
<thead>
<tr>
<th>Cluster</th>
<th>Description</th>
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<tbody>
<tr>
<td>Cluster 1</td>
<td>Mild Allergic Asthma&lt;br&gt;Early onset; atopic; normal lung function; ≤ 2 controller medications; minimal health care utilization; minimal sputum eosinophilia</td>
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<tr>
<td>Cluster 2</td>
<td>Mild-Moderate Allergic Asthma&lt;br&gt;Most common cluster; early onset; atopic; baseline FEV1 but reversible to normal; ≤ 2 controller medications; low health care utilization; infrequent need for oral corticosteroids; minimal sputum eosinophilia</td>
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<tr>
<td>Cluster 3</td>
<td>More Severe Older Onset Asthma&lt;br&gt;Older; very late onset; higher BMI (obese); less atopic; slightly decreased FEV1 with some reversibility; frequent need for oral corticosteroids; despite ≤ 3 controller medications including high doses of inhaled corticosteroids; minimal sputum eosinophilia</td>
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<tr>
<td>Cluster 4</td>
<td>Severe Variable Allergic Asthma&lt;br&gt;Older; atopic; severely decreased FEV1, but very reversible to near normal; high frequency of symptoms and advanced use; “variable” with need for frequent oral corticosteroids; high health care utilization; minimal sputum eosinophilia</td>
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<tr>
<td>Cluster 5</td>
<td>Severe Fixed Airflow Asthma&lt;br&gt;Older; longest duration; less atopic; severely decreased FEV1 with low reversibility (COPD similarities); high frequency of symptoms and advanced use; “fixed” with need for high doses of oral corticosteroids; high health care utilization; severe sputum eosinophilia and neutrophilia</td>
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**Asthma Cluster Analysis: 5 Clusters**

1. **Mild Allergic Asthma**<br>Early onset asthma (EOA); Normal lung function; atopic; ≤ 2 Controllers (medications used); Minimal Health Care Utilization (HCU); decreased sputum eosinophils (Eos)

2. **Mild-Moderate Allergic Asthma**<br>Most common cluster; EOA; Baseline normal FEV1 but reverses to normal; atopic; < 2 Controllers; Very low HCU, but some oral steroid use (HCU); ≤ decreased Eos)

3. **Severe Variable Allergic Asthma**<br>EOA, EOA; Severe decreased FEV1, but very reversible to near normal; Atopic (EOA); “Variable” with need for frequent HCU; High beta agonist use; EOA and global symptoms; High HCU and global symptoms (HCU); Increased Eos)

4. **Severe Fixed Airflow Asthma**<br>EOA; EOA; Severe decreased FEV1; Very atopic; High HCU; Atopic; Minimal health care utilization; High health care utilization; High sputum eosinophils and neutrophilia

**Asthma Cluster Analysis: 5 Clusters**

3. **More Severe Older Onset Asthma**<br>Older; Late onset (EOA); Higher BMI; Less atopic; Moderately low FEV1 with some reversibility; ≤ 2 Controllers (< 1 Deson); Higher HCU; More OCS; More OCS; Higher BMI; Increased HCU, Beta use and OCS; Increased Eos, EDI

5. **Severe Fixed Airflow Asthma (“COPD similarities”)**<br>Older; Longest duration; 65% female; Less atopic; Severely decreased FEV1 less reversibility; > 3 OCS; Higher BMI; more GAMS (H); High HCU, Beta use and OCS; Increased Eos, EDI

**Relationship of Guideline Asthma Severity Classification and Cluster Assignment (Clusters 1-5)**

Endotyping asthma: new insights into key pathogenic mechanisms in a complex, heterogeneous disease.

Anderson GP. Lancet 2008; 372: 1107-19

Creation of a New Taxonomy first requires an “Information Commons” in which data on large populations of patients become broadly available for research use and a “Knowledge Network” that adds value to these data by highlighting their inter-connectedness and integrating them with evolving knowledge of fundamental biological processes.

The plummeting cost of complete genome sequencing

Towards the $1000 genome

Development of a ‘stratified/ personalised’ medicine

‘Aspirational Goal’