Differentiating Difficult to Control vs. Severe Asthma

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HPI: 38 year old female with severe persistent asthma on chronic oral steroid therapy p/w increasing SOB and worsening wheezing.

Asthma history

Diagnosed with asthma at age 13

30-40 hospitalizations for asthma throughout her life

Endotracheal intubation X 1 for status asthmaticus

Chronic steroid dependence since 2003

Has been treated for contributing diseases

- *GERD, Allergic rhinitis (h/o nasal polyps)*

Current status:

- *Daily symptoms of shortness and wheezing, limited activity*
- *Use of rescue inhalers 6-8x/day*
- *Adherent with her medical regimen*
- *Treated with omalizumab for six years with reduction but not resolution of exacerbations*

***Past Medical History*:**

1.Severe Persistent Asthma
2. Allergic rhinitis
3. GERD
4. Fibromyalgia
5.Major Depressive Disorder

Allergies:

ASA- causes rash and wheezing

***Medications*:**

1.Methylprednisolone 16 mg daily
2.Fluticasone/Salmeterol 500/50 mcg inhalation b.i.d.
3. Montelukast 10 mg daily
4. DuoNebs as needed
5. Albuterol INH 3-4 times daily
6. Omeprazole 20 mg twice daily
7. Loratadine 10 mg daily
8. Fluticasone Nasal 1 puff twice daily
9.Calcium/Vitamin D
10. Alendronate 70 mg weekly
11. Xolair 300 mg SQ q 2 weeks

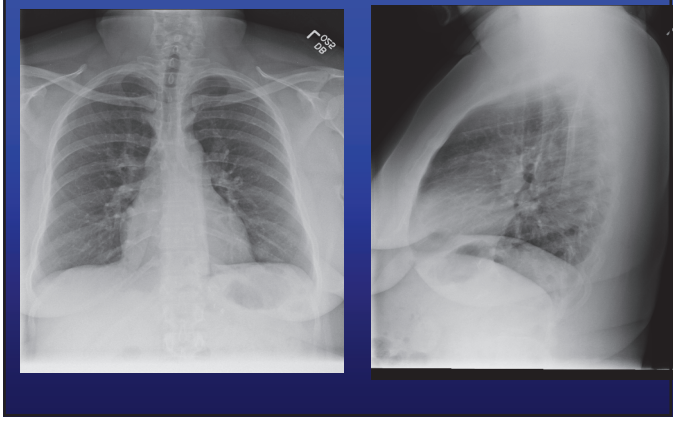
***Social History*:** Married with 3 children and husband, 2 dogs, outside cats, office work with no exposures, non-smoker.

***Family History*:**

mother with asthma and atopic dermatitis

***Physical Exam*:**

Pulmonary- prolonged expiration with moderate air movement and diffuse expiratory wheezing.



Pulmonary Function Testing:

	Ref	Best	% Pred
FVC	3.05	2.40	78%
FEV1	2.65	1.27	48%
FEV1/FVC	86	53	
FEF 25-75%	3.28	0.58	18%
PEF	5.78	2.89	50%
MVV	109	45	41%

What is Asthma?

Asthma is a chronic disease characterized by recurrent episodes of:

- wheezing,
- shortness of breath, and
- cough 2º to reversible airflow obstruction.

Bronchial Hyperresponsiveness &

Airway Inflammation are hallmarks of asthma.

Definition of Severe Asthma > age 6

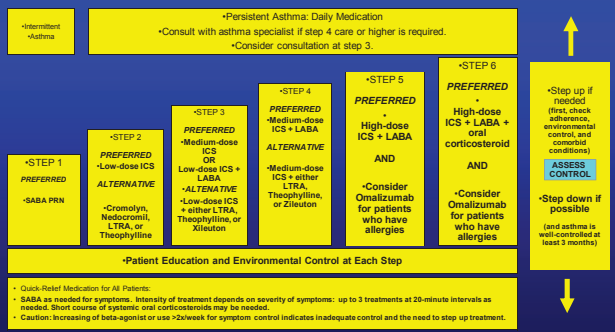
(ATS/ERS Guidelines; ERJ 2014;43:343)

Asthma which requires treatment with guidelines suggested medications for GINA steps 4–5 asthma (high dose ICS and LABA or leukotriene modifier/theophylline) for the previous year or systemic CS for > 50% of the previous year to prevent it from becoming ‘‘uncontrolled’’ or which remains ‘‘uncontrolled‘‘ despite this therapy

Assessing Asthma Control in Patients ≥12 Years of Age

Components of Control		Classification of Asthma Control (Youths ≥12 years of age and adults)		
		Well-Controlled	Not Well-Controlled	Very Poorly Controlled
Impairment	Symptoms	≤2 days/week	>2 days/week	Throughout the day
	Nighttime awakenings	≤2x/month	1-3x/month	≥4x/week
	Interference with normal activity	None	Some limitation	Extremely limited
	Short-acting beta$_2$-agonist use for symptom control	≤2 days/week	>2 days/week	Several times per day
	FEV_1 or peak flow	>80% predicted/ personal best	60-80% predicted/ personal best	<60% predicted/ personal best
	Validated questionnaires ATAQ ACQ ACT	 0 ≤0.75 ≥20	 1-2 ≥1.5 16-19	 3-4 N/A ≤15
Risk	Exacerbations	0-1 per year	2-3 per year	>3 per year
	Reduction in lung growth	Evaluation requires long-term follow-up care.		
	Treatment-related adverse effects	Medication side effects vary in intensity. Level of intensity does not correlate to specific levels of control but should be considered in overall assessment of risk.		

Stepwise Approach for Managing Asthma in Patients ≥ 12 Years of Age



NHLBI. National Asthma Education and Prevention Program. Full report of the Expert Panel: Guidelines for the diagnosis and management of asthma (EPR-3) DRAFT, page 517. Available at: http://www.nhlbi.nih.gov/guidelines/asthma/epr3/index.htm. Accessed February 9, 2007.

Challenges with Definition

ERS/ATS Severe Asthma Guidelines (ERJ 2014;43:343)

- Inherent in the definition of severe asthma is the exclusion of individuals who present with ‘‘difficult’’ asthma in whom appropriate diagnosis and/or treatment of confounders vastly improves their current condition.
- Therefore, it is recommended that patients presenting with ‘‘difficult asthma’’ have their asthma diagnosis confirmed and be evaluated and managed by an asthma specialist for more than 3 months.
- Thus, severe asthma according to the ATS/ERS definition only includes patients with refractory asthma and those in whom treatment of comorbidities such as severe sinus disease or obesity remains incomplete.

Contribution of Asthma Control to Definition of Severe Asthma

ERS/ATS Severe Asthma Guidelines (ERJ 2014;43:343)

Uncontrolled asthma defined as at least one of the following:

1) Poor symptom control: ACQ consistently > 1.5, ACT < 20 or "not well controlled" by NAEPP/GINA guidelines
2) Frequent severe exacerbations: two or more bursts of systemic corticosteroids (> 3 days each) in the previous year
3) Serious exacerbations: at least one hospitalization, ICU stay or mechanical ventilation in the previous year
4) Airflow limitation: after appropriate bronchodilator withhold FEV1 < 80% predicted (in the face of reduced FEV1/FVC defined as less than the lower limit of normal)

Controlled asthma that worsens on tapering of these high doses of ICS or systemic CS (or additional biologics)

Poor Control vs Severe Asthma

- Evidence of any one of these four criteria while on current high-dose therapy identifies the patient as having "severe asthma".
- Patients who do not meet the criteria for uncontrolled asthma, but whose asthma worsens on tapering of corticosteroids, will also meet the definition of severe asthma.
- Fulfilment of this definition predicts a high degree of future risk both from the disease itself (exacerbations and loss of lung function), as well as from side-effects of the medications.

Approach to Management/Contributing Factors/Co-Morbid Conditions

- **Examine for concomitant medical disorders, i.e. sinusitis/rhinitis, nasal polyps – 75-80% prevalence**
- **Obstructive Sleep Apnea**
- **Vocal Cord Dysfunction**
- **GERD - acid and non-acid reflux – 60-80% prevalence**
- **Obesity**
- **Steroid insensitivity – can be affected by co-morbidities or asthma itself**

Approach to Management/Contributing Factors/Co-Morbid Conditions

- Atopy/Environmental exposures
- Ongoing smoking vs. Asthma/COPD overlap
- Alternative diagnoses
- Psychological factors – Anxiety/ Depression – 25-49% prevalence
- Non-adherence
- Drugs: aspirin, non-steroidal anti-inflammatory drugs (NSAIDs), ß-adrenergic blockers, ACE inhibitors

Diagnoses Masquerading as Asthma in Adults

- Dysfunctional breathlessness/vocal cord dysfunction
- Chronic obstructive pulmonary disease
- Hyperventilation with panic attacks
- Bronchiolitis obliterans
- Congestive heart failure
- Adverse drug reaction (e.g. angiotensin-converting enzyme inhibitors)
- Bronchiectasis/cystic fibrosis

Diagnoses Masquerading as Asthma in Adults

- Hypersensitivity pneumonitis
- Hypereosinophilic syndromes
- Pulmonary embolus
- Herpetic tracheobronchitis
- Endobronchial lesion/foreign body (e.g. amyloid, carcinoid, tracheal stricture)
- Allergic bronchopulmonary aspergillosis
- Acquired tracheobronchomalacia
- Churg–Strauss syndrome

Diagnoses Masquerading as Asthma in Children

- Dysfunctional breathing/vocal cord dysfunction
- Bronchiolitis
- Recurrent (micro)aspiration, reflux, swallowing dysfunction
- Prematurity and related lung disease
- Cystic fibrosis
- Congenital or acquired immune deficiency
- Primary ciliary dyskinesia
- Central airways obstruction/compression

Diagnoses Masquerading as Asthma in Children

- Congenital malformations including vascular ring
- Tracheobronchomalacia
- Carcinoid or other tumor
- Mediastinal mass/enlarged lymph node
- Congenital heart disease
- Interstitial lung disease
- Connective tissue disease
- Foreign Body

Key Concepts

- Control: Significant activity of known disease
- If control poor on high dose medication, likely to have severe asthma
- Difficult asthma can suggest asthma or another diagnosis worsened by key co-morbid conditions

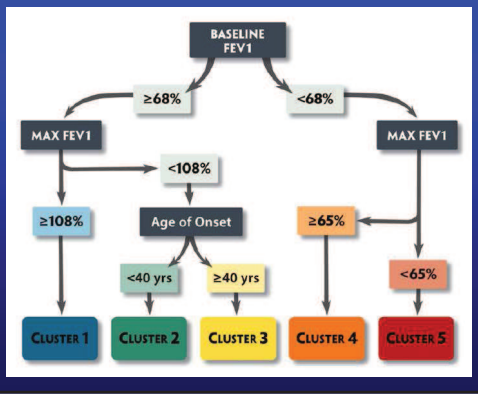
We have now moved to defining phenotypes of this heterogeneous disease

Clinical:
- Fixed obstruction
- Obese
- Adult onset
- Exacerbation prone
- Treatment resistant

Pathologic:
- Eosinophilic
- Non-eosinophilic
- Pauci-granulocytic

Triggers
- Occupational
- Aspirin
- Exercise
- Menses

Severe Asthma Clusters



Moore et al. AJRCCM 2010;181:315-323

Asthma Clusters

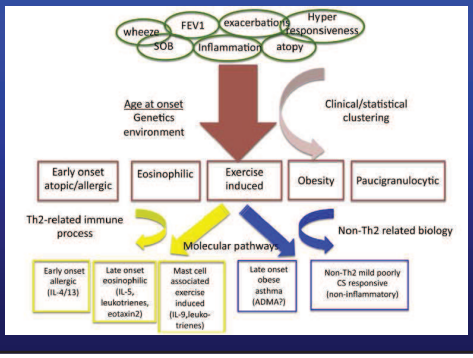
- Cluster 1: early onset, atopic, nl lung fxn ≤ 2 controllers, minimal healthcare utilization
- Cluster 2: early onset, atopic, ≥ 2 controllers, nl lung fxn, significant health care utilization
- Cluster 3: adult onset, obese woman with low lung fxn, high medication requirement and healthcare utilization
- Cluster 4: early onset, atopic, severe obstruction with some reversibility (FEV1: 57% to 76% pred), high healthcare utilization
- Cluster 5: early onset, severe obstruction, 66% atopic; less reversibility (FEV1: 43% to 58%), high health care utilization

Moore et al. AJRCCM 2010;181:315-323

Phenotype to Endotype?

- Phenotype suggests a clustering of characteristics, but may not describe underlying pathobiology that create these characteristics
- Endotype: underlying biologic or pathobiologic mechanism

Phenotypes to Endotypes



Pathological Phenotypes: Can they determine therapeutic choices?

- Eosinophilic/TH2 (IL-4, IL-5 and IL-13)
- Non-eosinophilic (sputum eos < 2%, or peripheral blood eos < 200/μl)

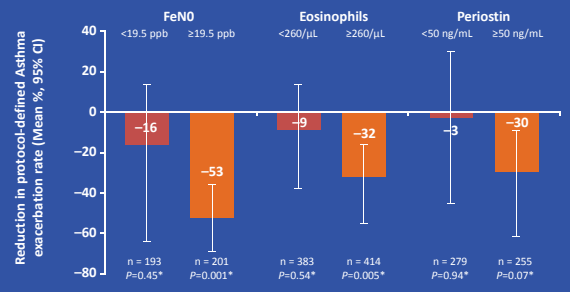
Biomarkers to identify the type 2 asthma phenotype

- Sputum eosinophils
- Exhaled nitric oxide
- Circulating eosinophils
- Periostin
- IgE
- Allergen skin testing
- Eosinophil Peroxidase?

Once we have identified a potential phenotype, what choices do we have?

How Does Omalizumab Compare With New Biologics In Similar Patients?

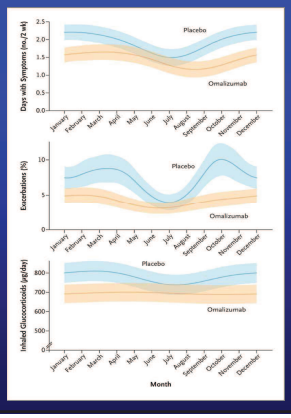
Effect of omalizumab based on type 2 inflammatory biomarkers



*Exacerbation reduction *P*-values; omalizumab versus placebo in each biomarker subgroup.

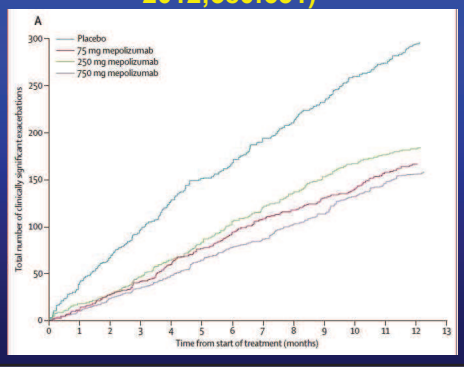
Hanania NA et al. *Am J Respir Crit Care Med.* 2013;187:804-811.

Seasonal Variation in Days with Symptoms, Frequency of Exacerbations, and Dose of Inhaled Glucocorticoids.



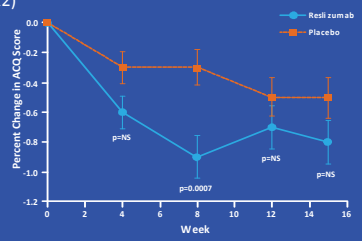
Busse WW et al. N Engl J Med 2011; 364:1005-1015

Mepolizumab (anti-IL-5) in Severe, Eosinophilic Asthma (Pavord et al. Lancet 2012;380:651)



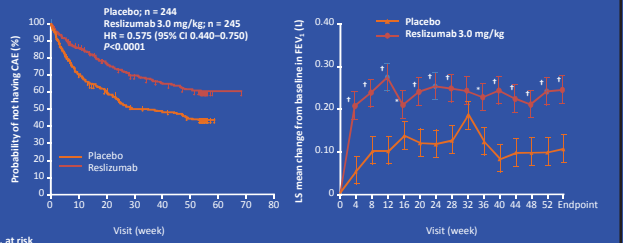
Reslizumab for Poorly Controlled Eosinophilic Asthma

- 106 patients randomized to reslizumab 3 mg/kg vs. placebo (IV dosing at weeks 0, 4, 8, and 12)
- Sputum eosinophil count reduced by 95.4% in reslizumab group vs. 38.7% in placebo group (*P*=0.0068)
- Mean change in FEV1 was –0.08 in the placebo group versus +0.18 in reslizumab group (*P*=0.0023)
- Exacerbations reduced (*P*=0.08)
- Greater change from baseline in patients with nasal polyps –1.0 vs. –0.1 with placebo (*P*=0.012)



Castro M et al. *Am J Respir Crit Care Med.* 2011;184:1125-1132.

Reslizumab—Effects on Exacerbations and Lung Function



No. at risk									
Placebo	244	169	138	112	107	97	0	0	0
Reslizumab	245	207	177	158	146	136	1	0	0

HR = hazard ratio; CI = confidence interval; LS = least square (mean).

Castro M et al. *Lancet Respir Med.* 2015;3:355-366.

34

Treatment options for the non-eosinophilic phenotype

- Macrolides
- Tiotropium – perhaps agnostic?
- Bronchial thermoplasty

Conclusions

- Severe asthma is a spectrum of disease, with different pathologic and clinical phenotypes.
- Determining the presence of difficult to control asthma is important as it can be driven by co-morbid conditions that require attention
- Individualizing therapy in asthma to achieve control, decreased exacerbations and high quality of life is the ultimate goal for our patients.