Therapeutic Interventions in Severe Asthma

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Objectives

- Discuss the definitions of severe and difficult to treat asthma
- Discuss features that can influence severe and difficult to treat asthma
  - Phenotypes
  - Genotypes
  - Biology and Biomarkers
- Discuss strategies to optimize treatment of asthma including the role of personalized medicine
What Is Severe Asthma?

WHO Definition

- Defined by the level of current clinical control and risks which can result in frequent severe exacerbations and/or adverse reactions to medications and/or chronic morbidity.

- 3 groups, each carrying different public health messages and challenges.
  - Untreated severe asthma
  - Difficult to treat asthma
  - Treatment resistant severe asthma
    - Controlled on high dose medication
    - Not controlled on high dose medication

Bousquet et al, JACI 2010
Intermittent Asthma

Persistent Asthma: Daily Medication
Consult with asthma specialist if step 4 care or higher is required.
Consider consultation at step 3.

Step 1
Preferred: Low-dose ICS
Alternative: Cromolyn, Nedocromil, LTRA, or Theophylline

Step 2
Preferred: Medium-dose ICS
OR
Low-dose ICS + LABA
Alternative: Low-dose ICS + either LTRA, Theophylline, or Zileuton

Step 3
Preferred: Medium-dose ICS + LABA
Alternative: Medium-dose ICS + either LTRA, Theophylline, or Zileuton

Step 4
Preferred: High-dose ICS + LABA
AND
Consider Omalizumab for patients who have allergies

Step 5
Preferred: High-dose ICS + LABA + oral corticosteroid
AND
Consider Omalizumab for patients who have allergies

Step 6
Preferred: High-dose ICS + LABA + oral corticosteroid + Omalizumab

Patient Education and Environmental Control at Each Step

Quick-Relief Medication for All Patients

• SABA as needed for symptoms. Intensity of treatment depends on severity of symptoms: up to 3 treatments at 20-minute intervals as needed. Short course of systemic oral corticosteroids may be needed.
• Use of beta$_2$-agonist >2 days a week for symptom control (not prevention of EIB) indicates inadequate control and the need to step up treatment.
Intermittent Asthma

Persistent Asthma: Daily Medication
Consult with asthma specialist if step 4 care or higher is required.
Consider consultation at step 3.

Step 1
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Alternative: Cromolyn, Nedocromil, LTRA, or Theophylline

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Step up if needed (first, check adherence, environmental control, and comorbid conditions)
Step down if possible (and asthma is well controlled at least 3 months)

Patient Education and Environmental Control at Each Step

Quick-Relief Medication for All Patients

- SABA as needed for symptoms. Intensity of treatment depends on severity of symptoms: up to 3 treatments at 20-minute intervals as needed. Short course of systemic oral corticosteroids may be needed.
- Use of beta₂-agonist >2 days a week for symptom control (not prevention of EIB) indicates inadequate control and the need to step up treatment.
Two Categories Of Treatment-resistant Severe Asthma

- Partially or poorly controlled asthma despite high dose ICS or high dose ICS-LABA combination and frequent or chronic use of systemic CS.
  - Previously been referred to as “refractory asthma” or “severe asthma"
  - In order for a patient to fall into this category, all reasonable efforts to eliminate other, non-asthma diagnoses must have been made.
- Patients with treatment-resistant severe asthma are considered to be relatively insensitive to either ICS or oral CS
Many Patients* Remain Uncontrolled On Standard ICS and LABA Therapy

Data From the GOAL Study

- Achieving control on FP + SM only
- Achieving control on FP only
- Achieving control on baseline plus OCS
- Percent remaining uncontrolled regardless of therapy

LABA=long-acting beta-agonist; FP=Fluticasone Propionate; SM=Salmeterol; OCS=Oral Corticosteroids.

*All patients received 500-1000 µg/d beclamethasone in previous 6 months.

Reasons for Non-responsiveness: Why Patients Are Difficult To Treat

- Poor compliance/adherence: Nearly 70% of patients fail to refill their ICS in the USA
- Environmental control issues: ETS, allergens, irritants
- Psychosocial and emotional factors
- Co-morbid aggravating conditions
- Pharmacologic response variables
  - Phenotypes (e.g. obesity)
  - Cigarette smoking
  - Genetics
  - Variable pathogenic dominant pathway
Factors That Impact Asthma Severity And Control

- Asthma severity may be influenced by genetic and environmental factors, underlying disease activity and patient's disease pathobiological processes which differs between patients with differing phenotypes.
What Are The Potential Approaches For Optimizing Asthma Treatment?

- Adherence
- Environmental control
- Education on medications and the disease
- Matching the correct drug to the patient:
  - Pharmacogenetics
  - Phenotypes/Endotypes
  - Biomarkers
- New and improved medications
Drug Response Profile

Number of Patients

POPULATION RESPONSE PROFILE

Deteriorated

Improved

Zero Response
Patient Responsiveness to ICS and LTRA Is Highly Variable

Neither medication (55%)

22% Patients respond to montelukast

40% Patients respond to fluticasone

Analysis of Inhaled Corticosteroid Partial- and Non-Responders

Patients (%)

FEV₁ % Change from Baseline

Response To ICS May Be Genetically Determined: Effects Of CRHR1 Genotype


Change in FEV<sub>1</sub> with 8 Wks ICS Therapy (%)

- **GAT/GAT Homozygous Haplotype**
  - CAMP study: 21.8%*
  - Adult study: 13.7%†

- **Non-GAT Haplotype**
  - CAMP study: 7.4%
  - Adult study: 5.5%

* $P<0.02$ vs non-GAT.
† $P<0.01$ vs non-GAT.
The *Transition* to Phenotyping And Endotyping

"Asthma"

- **Symptoms**
  - Exacerbations
  - FEV1

- **Th2 inflammation**
  - Early onset/allergic
  - Late onset eosinophilic
  - Obese
  - Neutrophilic

- **No/less Th2 inflammation**
Endotyping: “Th2-Lo Asthma”

- Defined as “apparent” absence of Th2
- Much less well defined than Th2-Hi
- Generally adult onset
- May include obesity-related, post infectious, neutrophilic, smoking related…
- *All* associated with poor CS response
In Untreated Pts, No Eos Associated With Obesity, Low IgE And Poor Steroid Response

Adapted from McGrath AJRCCM 2012
Influence Of BMI On Asthma Control Days: Comparison Of Montelukast Vs. Budesonide

M. Peters-Golden, ERJ, 2006
Cigarette Smoking and Asthma Variability: Reduced Response to Oral Corticosteroids

![Graph showing FEV1 and Asthma Control Score for Smokers, Ex-Smokers, and Never-Smokers with data points for Placebo and Prednisolone.](image)

Endotyping: Th2-Hi Asthma

- Atopy/IgE (probably worst indicator)
- Early age at onset
- Blood/Lung eosinophilia
- Exhaled NO (FeNO)
- Mast cells
- Gene profiles/biomarkers (periostin)
Are There Variable Responses To Th2 Immunomodulators As Well?

• Due to the heterogeneity of asthma, it is inevitable that distinct dominant pathogenic mechanisms exist (e.g. eosinophil/IL-5 or IgE dominant inflammation).

• Finding which pathogenic factor(s) are important in individual patients is a challenge in treating severe asthma.

• A broad spectrum immunomodulator approach for all patients is problematic due to potential adverse consequences.
Immunomodulators for Asthma

IL-4, IL-13, Anti-IL-13, Anti-IL-4Rα, Anti-IL-4

IL-5, GMCSF, IL-2Rα

CD40, CD40L, B cell

FCεRII, Plasma Cell

IgE, Mediators, Cytokines

Anti-IL-5

Bone Marrow, CCR

Eosinophil

IL-9

TNF-α

VLA-4, ICAM

Blood Vessel

VCAM-1

Airway Inflammation
Role of Anti IL-5 in Asthma

• Several older studies confirmed reductions in blood & sputum eos w/o significant changes in AHR, lung function or symptoms

• 2 NEJM studies (March, 2009):
  – Unlike previous studies, high sputum eosinophils, >3% required (<5% of uncontrolled asthma patients)
  – Reduction of eosinophils
  – Had no/modest effect on FEV1, AHR or symptoms
  – Significantly reduced exacerbations

• Recent Lancet paper inclusion criteria (70%):
  – Sputum eos >3%, FeNO>50, blood eos >300, deterioration of asthma after <25% reduction in ICS or OCS
  – >2 asthma exacerbations in previous year
Mepolizumab for Severe Eosinophilic Asthma

- ~50% reduction in exacerbations/patient/year
- No effects on FEV1, ACQ or AQLQ

Pavord et al, Lancet 2012
Th2 (IL-4, -5, -9, -13) Cytokine Inhibitors

• Anti-IL-4 strategies alone not very successful
  – Strategies aimed at both IL-4 and IL-13 may be better option

• MAb aimed at IL-9: Failed to meet endpoints...D/C

• Mono-specific IL-13 strategies initially had disappointing results despite IL-13’s putative importance in AWH, mucus, AWR, IgE, eotaxin production, etc.
  – Several new studies have shown good results
Airway Epithelial Periostin

- Up-regulated in bronchial epithelial cells of asthmatic subjects
  - Increased by IL-13
- Autocrine effects: activation of TGF-β and up-regulation of type I collagen
- Paracrine effects: TGF-β–mediated incr in type I collagen production in fibroblasts
- Likely contributes to incr airway fibrosis and decr airway distensibility

Sidhu et al. PNAS, 2010
Lebrikizumab Treatment in Adults with Asthma: Study Design

J Corren et al, NEJM, 2011
Lebrikizumab Treatment in Adults with Asthma

J Corren et al, NEJM, 2011
IL-4Rα Receptor Blockers: IL-4 and IL-13 Binding Site

- Pitrakinra (Aerovant): 14 kDa IL-4 mutein vs. IL-4Rα
First “Real World” Study With Pitrakinra

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- **Run-In**
- **Stabilization**
- **LABA/ICS withdrawal**
- **Post**

**Inhaled pitrakinra or placebo**
Pitrakinra

- Better effects in patients with:
  - High Blood eos (>350)
  - Certain SNPs at 3’ end of IL4RA

Slager et al, JACI, 2012
Immunomodulators for Asthma

- **IL-4**
- **IL-13**
- **IL-2Rα**
- **IL-5**
- **GMCSF**
- **CD40**
- **CD40L**
- **B cell**
- **IL-4Rα**

**Mediators**

- **Cytokines**
- **Airway Inflammation**
- **IL-9**

**Cells and Structures**

- **Tcell**
- **APC**
- **Plasma Cell**
- **FcεRII**
- **IgE**
- **Omalizumab**
- **Bone Marrow**
- **Eosinophil**
- **VLA-4**
- **ICAM**
- **Blood Vessel**
- **VCAM-1**

**Networks and Interactions**

- **CD40**
- **CD40L**
- **IL-4**
- **IL-13**
- **IL-2Rα**
- **GMCSF**
- **IL-5**
- **B cell**
- **Plasma Cell**
- **FcεRII**
- **IgE**
- **Omalizumab**
- **Eosinophil**
- **Blood Vessel**
- **Airway Inflammation**
Omalizumab Indications

• Moderate to severe persistent asthma in patients with a positive skin test or in vitro reactivity to a perennial aeroallergen and symptoms that are inadequately controlled with ICS+/-LABA.
Asthma Exacerbations Over 48 Weeks In EPR3 Step 5/6

Omalizumab and Seasonal Asthma Exacerbations In 6 to 20 y/o

NEJM, 3/11
Factors Predictive Of Clinical Response

• Reasons for omalizumab being ineffective for some (~40%) patients are unknown.

• Improvements correlate w/ IgE reductions, BUT free IgE levels in nonresponders are similar to those found in responders\(^1\)

• Possible reasons:\(^2\)
  (1) Relationship between free IgE levels and Fc\(\varepsilon\)R1 expression
  (2) Ratio of specific IgE to total IgE
  (3) Intrinsic cellular sensitivity.

• Recent data indicate that response at 16 wks is highly predictive of persistent response at 32 wks\(^3\)

Omalizumab and Asthma Summary

- Omalizumab is effective in children and adults in reducing exacerbations and steroid requirements
  - Also positive effects on SABA use, QOL, Sxs and PFTs (minor)
- Omalizumab has anti-inflammatory effects
- If not effective by 4-6 months, probably will not be effective
  - Predictors of who will respond are unclear
- Whether omalizumab can be stopped with sustained clinical efficacy is unclear
  - May depend on duration of treatment
Allergic Asthma

Severe

Childhood

Adult

Severity

Age at onset

Wenzel, Nat Med 2012
Critical Issues for Immunomodulators

- Many options for the same or similar patient population.
- Which will provide better therapeutic options?
  - Phenotype/Endotype (Biomarker) driven?
  - Decrease sxs & exacerbations & improve QOL
  - True Immunomodulation: prevent/alter disease course
- Cost effective
- Have favorable risk/benefit ratio

Too Powerful
Broad-spectrum

Too Weak
Very Specific
Severe Asthma Management Paradigm

Adherence

Disease Control

Achieve Goals

↓ Morbidity

↓ Mortality

↓ Economic Burden

Environmental Modification

- Irritant
- Allergen

Occupational Trigger

Evidence-Based Decision Making

Phenotype Decision Making

Cost-Effectiveness

Pharmacogenetics

Manage Comorbidities

- CRS
- GERD

Appropriate Pharmacotherapy

Cost-Effectiveness

Pharmacogenetics

ASA Sens

Monitoring Asthma Control

Disease Variability

↓ Morbidity

↓ Mortality

↓ Economic Burden
Conclusions

• Severe asthma is a major public health issue that causes significant morbidity and mortality.

• What Is Needed To Improve Care Of Patients With Severe Asthma?
  – Cluster analyses and biomarkers identifying different phenotypes important in defining pharmacologic responses
  – Identification of novel genetic variants that contribute to response heterogeneity
  – Identification of new therapies that have favorable risk/benefit ratios and are immunomodulating:
    • Permanently Reprogram the immune system to ignore “insignificant” threats without compromising its ability to respond to real threats
Personalized Medicine

Is your inhaler right for you?

β16 AsthmaGEN™
the beta-agonist drug response test

brought to you by Consumer Genetics, Inc.
www.consumergenetics.com