

The Pharmacist's Role in Managing Severe Asthma

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Educational Objectives

At the completion of this activity, the participant will be able to:

- Examine the current guidelines for asthma treatment
- Discuss treatment strategies for severe asthma
- Explore the current biologics for asthma treatment (based on the various mechanisms of action and phenotypes) that are approved and in clinical development
- Identify strategies to provide patient counseling for patients with severe asthma being treated with biologic therapy

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Asthma Burden of Illness

- 300 million worldwide have asthma
- 40 million Americans (12.9%) were diagnosed with asthma in 2014
- Approximately 7.4% US adults
- Black Americans are 2-3 times more likely to have an asthma-related death than any other race
- Increases risk of arthritis, heart disease, cancer, diabetes, and hypertension
- Each additional comorbid condition increases asthma symptom episodes, activity limitation, sleep disturbances, and ED visits

National Center for Health Statistics. CDC website. www.cdc.gov/nchs/nhanis/2011-14/nhanac-1.htm. Updated March 1, 2016. Centers for Disease Control and Prevention. Asthma's impact on the nation: data from the CDC National Asthma Control Program. CDC website. http://www.cdc.gov/asthma/asthma_national_asthma_control_program.html. Updated March 2016. Frank MB, et al. Ann Am Thorac Soc. 2015;12(2):454-61. Global Initiative for Asthma. 2017. <http://ginasthma.org/2017-gina-report-global-strategy-for-asthma-management-and-prevention/>.

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Definition of Asthma

- Well controlled
- Not well controlled
- Very poorly controlled
- Intermittent
- Persistent
 - Persistent asthma is stratified as mild, moderate, or severe
- Persistent, chronic disease leads to progressive inflammation and edema and mucus hypersecretion
 - Untreated, structural changes may lead to airway remodeling
 - May see reduced responsiveness to usual therapies over time

Global Initiative for Asthma. 2017. <http://ginasthma.org/2017-gina-report-global-strategy-for-asthma-management-and-prevention/>. National Heart, Lung, and Blood Institute. Expert panel report 3: guidelines for the diagnosis and management of asthma. NIH website. <http://www.ncbi.nlm.nih.gov/books/ NBK129874/>

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Clinical Presentation of Asthma

- Wheeze, SOB, chest tightness, cough, and expiratory airflow limitation
- Symptoms and airflow limitation vary over time and in intensity
- Affected by precipitating factors
- May resolve spontaneously or with medication
- Airway hyperresponsiveness typically persists, even without symptoms or when lung function is normal, but may resolve with treatment
- Exacerbations may be life-threatening
 - Significant patient and health care burden

SOB = shortness of breath.

Global Initiative for Asthma. 2017. <http://ginasthma.org/2017-gina-report-global-strategy-for-asthma-management-and-prevention/>.

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Nonpharmacologic Interventions

- Cessation of smoking and avoid second-hand smoke exposure
- Exercise
- Avoid triggers
 - Occupational exposure
 - Medications that may aggravate asthma
 - Indoor allergens
 - Outdoor allergens
- Weight reduction
- Vaccinations
- Address emotional stress
- Immunotherapy



Global Initiative for Asthma. 2017. <http://ginasthma.org/2017-gina-report-global-strategy-for-asthma-management-and-prevention/>.



Pharmacologic Interventions

- Quick relief
 - Short-acting beta agonist (SABA)
- Long-term controller
 - Inhaled corticosteroid (ICS)
 - Long-acting beta agonist (LABA)
 - Leukotriene antagonist (LKTA)
 - Tiotropium
 - Oral corticosteroids
 - Biologic products



Global Initiative for Asthma. 2017. <http://ginasthma.org/2017-gina-report-global-strategy-for-asthma-management-and-prevention/>.



Asthma Guidelines (≥12 years old)

Type of Asthma	Quick Relief	Long-Term Controller
Step 1	As needed SABA	None
Step 2		Low-dose ICS <i>LTRA, low-dose theophylline</i>
Step 3		Low-dose ICS + LABA Medium-high dose ICS <i>Low dose ICS + LTRA (or +theophylline)</i>
Step 4		Medium- to high-dose ICS + LABA Add tiotropium <i>High-dose ICS + LTRA</i>
Step 5		High-dose ICS + LABA Referral for anti IgE or anti IL-5 <i>Low oral steroid (prednisone ≤7.5 mg/day)</i>



Global Initiative for Asthma. 2017. <http://ginasthma.org/2017-gina-report-global-strategy-for-asthma-management-and-prevention/>.
National Heart, Lung, and Blood Institute. Expert panel report 3: guidelines for the diagnosis and management of asthma. NHLBI website. <https://www.nhlbi.nih.gov/files/docs/public/asthma/guidelines.pdf>.



Goal Evaluation



Achieve control

- Symptoms, rescue inhaler use, controller dose, activity, triggers, lung function, diagnosis, patient choice

Reduce risks

- Instability, lung function, exacerbations, medication adverse effects



Global Initiative for Asthma. 2017. <http://ginasthma.org/2017-gina-report-global-strategy-for-asthma-management-and-prevention/>.



Unmet Needs

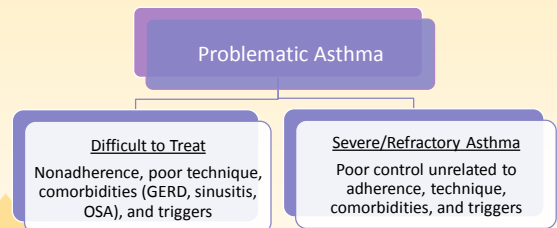
- Approximately 11 million Americans (44.7%) had asthma exacerbations (2014 data)
 - 1.8 million ED visits (2011 data)
 - 3651 deaths (2014 data)
- Nonadherence with controller agents increases risk of worsening asthma and likelihood of asthma exacerbations
- Suboptimal adherence to prescribed controller medications linked to difficult-to-control asthma
- Prevalence of severe asthma is 5%-10% of all patients with asthma



National Center for Health Statistics. 2014. CDC website. <http://www.cdc.gov/asthma/nchs2014/asthma2-1.htm>. Updated March 1, 2016. US Department of Health & Human Services. CDC website. http://www.cdc.gov/asthma/news_recent_data.htm. Updated April 14, 2016. Murphy AC, et al. Thorax. 2012;67(3):351-353. AAAAI website. <https://www.aaaai.org/global/latest-research-summaries/News-Research-Item-2012-03-01/Prevalence-of-severe-asthma>.



Severe Asthma Definition and Management



Global Initiative for Asthma. 2017. <http://ginasthma.org/2017-gina-report-global-strategy-for-asthma-management-and-prevention-AAAAA-website>. <https://www.aaaai.org/global/latest-research-summaries/News-Research-Item-2012-03-01/Prevalence-of-severe-asthma>.



Management of Severe Asthma

- Optimize ICS/LABA dose (high dose)
 - Ex: budesonide (>800 mcg), fluticasone (>500 mcg), mometasone (>440 mcg)
- Add low-dose maintenance oral corticosteroids (≤7.5 mg prednisone daily)
- Tiotropium improves lung function, prolongs time to exacerbation
- Leukotriene receptor antagonists (aspirin-sensitive)
- Phenotype-guided add-on treatment (IgE antagonist, IL-5 antagonist)
 - Step 5, GINA guidelines 2017
 - SC omalizumab
 - SC mepolizumab
 - IV reslizumab

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Global Initiative for Asthma, 2017. <http://ginasthma.org/2017-gina-report-global-strategy-for-asthma-management-and-prevention/>

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Most Common Clinical Asthma Phenotypes

Type	Features
Allergic	Typically begins in childhood Past/family history of allergy (eczema, allergic rhinitis, food or drug allergy) Induced sputum may reveal eosinophilic airway inflammation
Non-allergic	Sputum may be neutrophilic, eosinophilic, or with few inflammatory cells Responds less well to ICS
Late-onset	More common in women Non-allergic May require higher doses of ICS (relatively refractory)
Fixed airflow limitation	Long-standing asthma develops into fixed airflow limitation likely due to airway wall remodeling

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Global Initiative for Asthma, 2017. <http://ginasthma.org/2017-gina-report-global-strategy-for-asthma-management-and-prevention/>

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Patient Case

YL is a 44-year-old female presenting to the community pharmacy for advice on how to improve her asthma control

- **CC:** Persistent wheezing despite current therapy
- **HPI:** Restricted physical activity secondary to worsening asthma and wheezing. She was admitted several times over the past 3 months for asthma exacerbations and had multiple emergency room visits. She is concerned that her asthma is making it difficult to care for her children and ill father and is seeking advice from the pharmacist for how to get better control
- **PMH:**
 - Severe, persistent asthma x 5 years (asthma diagnosed 30 years ago)
 - Allergic rhinitis

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Current Medications and Questions

Current medications and lab results

- Fluticasone 500 mcg/salmeterol 50 mcg 2 inhalations twice a day
- Albuterol inhaler (received a refill 3 weeks ago)
- Multiple prednisone tapers
- OTC: Loratadine daily, acetaminophen daily for headaches
- Weight: 85 kg; height: 5'4"
- Asthma Control Test: 7 (Low)
- Serum eosinophils 410/uL serum IgE 450 IU/mL
- Allergen testing + cat dander and dust mites
- Physical exam revealed bilateral wheezing in upper lung fields
- PFTs: FEV1 50% predicted by age

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Does YL Have Difficult-to-Treat or Severe Asthma?

- Assess technique
- Assess comorbidities
- Assess vaccinations
- Assess dose of ICS
- Assess trigger management (allergy testing)
- Assess refill rates
- Assess patient preference

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Biologic MOA Basics and the IL Pathway

IL-4	<ul style="list-style-type: none"> • Critical component for TH2 cell differentiation • Overlapping role with IL-13
IL-5	<ul style="list-style-type: none"> • Promotes eosinophilic recruitment, survival, and activation
IL-13	<ul style="list-style-type: none"> • Promotes cell influx, airway responsiveness and remodeling • Overlapping role with IL-4
IgE	<ul style="list-style-type: none"> • Receptor located on mast and basophils

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Approved Biologics for Severe Asthma

Omalizumab

- IgG1 kappa monoclonal antibody that binds IgE

Mepolizumab

- IL-5 antagonist monoclonal antibody

Reslizumab

- IL-5 antagonist monoclonal antibody

Nucala (mepolizumab) package insert, GlaxoSmithKline, Research Triangle Park, NC, Feb 2017. Xolair (omalizumab) package insert, Genentech USA, Inc. South San Francisco, CA and Novartis Pharmaceuticals Corporation, East Hanover, NJ, July 2016. Cinqair (reslizumab) package insert, Teva Respiratory, LLC Frazer, PA, May 2016.

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Comparisons of Approved Biologics

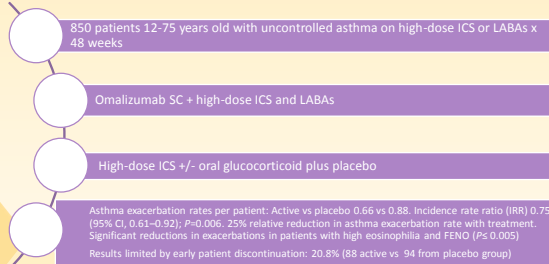
Biologic Agent	Indication	Dosing
Omalizumab	Moderate to severe persistent "allergic" asthma ≥6 years old with a positive skin test or in vitro reactivity to perennial aeroallergen and symptoms inadequately controlled on ICS	75 to 375 mg subcutaneously (SC) Q2 or 4 weeks Dose and frequency adjusted by IgE (IU/mL) and body weight using dose determination charts
Mepolizumab	Add-on maintenance ≥12 years, with eosinophilic phenotype	100 mg SC Q4 weeks
Reslizumab	Add-on maintenance, ≥18 years, with eosinophilic phenotype	3 mg/kg IV Q4 weeks over 20-50 minutes

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Nucala (mepolizumab) package insert, GlaxoSmithKline, Research Triangle Park, NC, Feb 2017. Xolair (omalizumab) package insert, Genentech USA, Inc. South San Francisco, CA and Novartis Pharmaceuticals Corporation, East Hanover, NJ, July 2016. Cinqair (reslizumab) package insert, Teva Respiratory, LLC Frazer, PA, May 2016.

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Omalizumab: EXTRA Trial



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Hatawara NA, et al. Ann Intern Med. 2011;154:573-582.

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Omalizumab Biomarkers?

- EXTRA study post-hoc analysis of low- and high-biomarker subgroups
 - Higher percentage of females in biomarker subgroups
- Biomarker and predictors of Th2 mediated inflammation (treatment effect)
 - Greater benefits in patients with:
 - Higher FE_{NO} at baseline
 - Higher baseline blood eosinophil counts
 - Higher baseline periostin
- Unable to demonstrate that specific-to-total IgE ratios, serum tryptase, eosinophil cationic protein, or soluble CD23 were predictive
- Additional studies required to determine role/value of these biomarkers

Pharanda NA, et al. Am J Respir Crit Care Med. 2013;187(8):804-811.

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Omalizumab Adverse Reactions and Cautions

- Most common adverse effects:
 - arthralgia, general pain, leg/arm pain, fatigue, dizziness, fracture, pruritus, dermatitis, and earache
- Malignancy?
- Do not abruptly discontinue corticosteroids
- Fever, arthralgia, and rash
- Eosinophilia, vasculitic rash, worsening pulmonary symptoms, cardiac complications, and/or neuropathy, especially with oral corticosteroid dose reductions
- CV- and CBV-related concerns added to adverse effects
- Black box warning
 - Anaphylaxis (bronchospasm, hypotension, syncope, urticaria, and/or angioedema of throat or tongue) reported

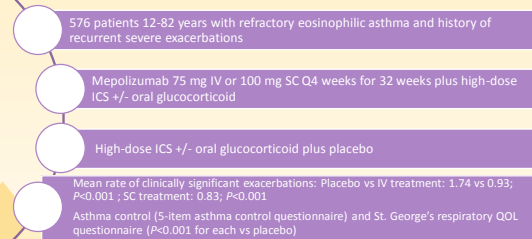
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Xolair (omalizumab) package insert, Genentech USA, Inc. South San Francisco, CA and Novartis Pharmaceuticals Corporation, East Hanover, NJ, July 2016 and FDA Drug Safety communication: <https://www.fda.gov/oc/oc/2016/07/2016-07-20-omalizumab-safety-communication>

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Mepolizumab MENZA Trial

"Mepolizumab as Adjunctive Therapy in Patients with Severe Asthma"



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Cheng HZ, et al. N Engl J Med. 2014;371:1186-1207

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Mepolizumab: SIRIUS Trial “Steroid Reduction with Mepolizumab Study”

- 135 patients with severe eosinophilic asthma
≥300 cells/mL prior to study or ≥150 cells/mL during optimization
- Optimize steroid regimen, induction and reduction in steroid dose and maintenance
- Mepolizumab subcutaneous versus placebo
- Steroid dose reduction: OR 2.39 (95% CI, 1.25–4.56) $P=0.008$ and steroid daily dose reduced ≤5 mg: 32% vs 54% active vs placebo and OR 2.45 (95% CI, 1.12–5.37) $P=0.02$.
No exacerbations needing hospitalization in treatment group (vs 7 in placebo group).
Adverse effects similar between groups

Bell DT, et al. N Engl J Med 2014;371:1189-97.

Mepolizumab Adverse Reactions and Cautions

- Most common adverse reactions
 - Headache, injection site reaction, back pain, and fatigue
- Hypersensitivity reactions
 - Anaphylaxis, angioedema, bronchospasm, hypotension, urticaria, rash
- Herpes zoster infections
 - Consider vaccination prior to starting therapy
- Do NOT abruptly stop oral or ICS
 - Decrease gradually
- Treat patients with pre-existing helminth infections before beginning therapy
- Caution in pregnancy and lactation

Nucala (mepolizumab) package insert, GlaxoSmithKline, Research Triangle Park, NC, Feb 2017

Reslizumab: Breath Program

- 106 patients aged 18-75 years with poorly controlled eosinophilic asthma
- Reslizumab (3.0 mg/kg) infusion or placebo at weeks 4, 8, and 12
- Placebo at weeks 4, 8, 12
- Mean change in ACQ scores were -0.7 and -0.3 in treatment vs placebo groups, respectively ($P=0.0541$)
Significant differences seen when adjusted for ACQ scores >2 ($P=0.0505$) and nasal polyps ($P=0.0119$)

Casbo M, et al. Am J Respir Crit Care Med 2011;184:1120-1132

Reslizumab: Breath Program

- 265 patients inadequately controlled with blood eosinophil count ≥400 cells/μL (surrogate for sputum eosinophils ≥3%)
- Reslizumab (3.0 mg/kg) or (0.3 mg/kg IV) or placebo at weeks 4, 8, and 12
- Placebo
- Change in FEV₁ increased with reslizumab 0.3 mg/kg IV (115 mL; $P=0.0237$) and 3.0 mg/kg IV (160 mL; $P=0.0018$) vs placebo. Asthma symptoms and quality of life also improved

Bjerner L, et al. Chest 2016; 150(4):789-798

Reslizumab Adverse Effects and Cautions

- Most common adverse reaction
 - Oropharyngeal pain
- Black Box Warning
 - Anaphylaxis
- Malignancy
- Reduction in corticosteroid dosage
 - Decrease corticosteroids gradually, if appropriate
- Parasitic (helminth) infection
 - Treat patients with pre-existing helminth infections prior to starting therapy

Cinpep (reslizumab) package insert, Terna Respiratory, LLC Frisco, PA, May 2016.

Outcomes Summary of Biologic Treatments for T_H2/Type 2-High Asthma

Target	Drugs	Outcome
IgE	Omalizumab	Decrease in early and late asthmatic responses in allergic asthma; decrease in serum IgE
IL-4 and IL-13	Dupilumab*, lebrikizumab*, tralokinumab*	Decrease in asthma exacerbations, decrease FE _{NO} , decrease in SABA use, increase in FEV ₁
Anti-IL-5	Mepolizumab, reslizumab	Decrease asthma exacerbations, decrease in blood/sputum eosinophils, increase in FEV ₁
Anti-IL-5R alpha	Benralizumab*	Decrease in eosinophils in airway mucosa, sputum, bone marrow and blood

T_H2 = T helper cell type 2
*Investigational biologic agent

Fall ML, et al. J Allergy Clin Immunol 2016; 137:259-310

Investigational Agents

- Lebrikizumab (monoclonal antibody against IL-13)
- IMA-638 (neutralizing antibodies that prevent attachment of IL-13)
- Pitrakirra (IL-4 variant that blocks IL-4 and IL-13 blocker)
- Dupilumab (monoclonal antibody prevents IL-4 and IL-13 binding)
- MT203 (monoclonal antibody against GM-CSF)
- AMG 157 (blocks TSLP)
- Altrakincept (soluble recombinant human IL-4R)
- Pascolizumab (humanized monoclonal antibody against IL-4)
- IMA-026 (neutralizing antibodies that prevent attachment of IL-13)
- AMG 317 (monoclonal antibody prevents IL-4 and IL-13 binding)
- Infliximab and golimumab (TNF blockers)

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Role of Pharmacist in Moderate to Severe Asthma Care

- Appropriate technique
- Ask patient about personal treatment goals
- Prevention of exacerbations
- Individualize care
 - Consider insurance, medication availability, cultural and personal preferences and health literacy
- Create Asthma Action Plans
- Address adherence concerns
- Educate patients on add-on therapies

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Poor Medication Adherence

Factors contributing to poor adherence	How to identify poor adherence in practice
Medication/regimen factors <ul style="list-style-type: none"> • Difficulty using inhaler device • Burdensome regimen • Multiple types of inhalers 	Ask an empathetic question <ul style="list-style-type: none"> • Acknowledge likelihood of incomplete adherence and encourage an open, nonjudgmental discussion
Unintentional nonadherence <ul style="list-style-type: none"> • Misunderstood instructions • Forgetfulness • Absence of daily routine • Cost 	
Intentional nonadherence <ul style="list-style-type: none"> • Perception that treatment unnecessary • Denial/anger about diagnosis or treatment • Inappropriate expectations • Concerns about adverse effects • Dissatisfaction with providers • Stigmatization • Cultural or religious issues • Cost 	Check medication use <ul style="list-style-type: none"> • Date of last controller prescription • Date and dose counter on inhaler

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Successful Adherence Interventions

- Shared decision making for medication/dose choice
- Inhaler reminders for missed doses
- Prescribing ICS once daily versus twice daily
- Medication reminder mobile phone applications
- Diary or journal to keep track of symptoms and medication use
 - Phone apps for tracking

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Self-Monitoring of Symptoms and Peak Flow

- Track symptoms (with or without a diary)
 - Take action if necessary when symptoms start to worsen
- Peak expiratory flow (PEF) for:
 - Monitoring post-exacerbation changes
 - Monitoring response to treatment change
 - Objective evaluation if symptoms are excessive
 - Identification of triggers
 - Guide detection of airflow limitation
 - Early recognition of exacerbations
 - Severe asthma

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Creating Asthma Action Plans

- Individualized short-term treatment changes that can be made by the patient in response to changes in symptoms and/or PEF
- Alert patient about how and when to access medical care
- Empower patient
- Can also be used by health care providers to guide therapy
- Guidelines give instructions on how to develop
- Many templates available online

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Biologic-Related Patient Counseling

- Prior authorization/insurance issues
- Collaborating with specialty pharmacist
- Vaccination contraindications and recommendations
 - AVOID live vaccinations (zoster, intranasal flu during treatment)
- Recognize delayed reactions to treatment and how to react (anaphylaxis)
- Dispense product with medication guide
- Educate on onset of action and expected results
- Inform if planning on pregnancy or become pregnant
- Not for acute management

Conclusion

- 300 million individuals worldwide have asthma
- Evidence-based guidelines drive care management
- Exacerbations, hospitalizations, and emergency room visits still high
- Pharmacists may impact both difficult-to-treat and severe asthma metrics
- Role of pharmacist
 - Education
 - Medication adherence
 - Asthma action plan
 - Application of evidence-based treatments
 - Referral

Additional Resources

Resource	Website
Asthma Action Plan Templates National Heart Lung and Blood Institute	https://www.nhlbi.nih.gov/files/docs/public/lung/asthma_actplan.pdf
Asthma and Allergy Foundation of America What Are the Symptoms of Asthma?	http://www.aafa.org/page/asthma-symptoms.aspx
Severe Asthma Research Program (SARP) National Institutes of Health/ National Heart, Lung & Blood Institutes sponsored network	http://www.severeasthma.org/