

Diagnosis and Management of Asthma: Insights from the Global Initiative for Asthma (GINA) and AAAAI Recommendations

Asthma is a chronic respiratory condition characterized by airway inflammation, bronchoconstriction, and variable airflow obstruction, leading to symptoms such as wheezing, shortness of breath, chest tightness, and cough. The Global Initiative for Asthma (GINA) provides comprehensive guidelines for the diagnosis and management of asthma, aiming to improve patient outcomes and quality of life. Similarly, the American Academy of Allergy, Asthma & Immunology (AAAAI) offers additional recommendations that align with and complement GINA guidelines. This post will outline key aspects of these guidelines, focusing on the diagnostic process and management strategies.

Diagnosis of Asthma

Diagnosing asthma involves a combination of clinical assessment, pulmonary function testing, and consideration of differential diagnoses. Both GINA and AAAAI recommend the following approach:

Clinical Assessment

1. **Medical History:** A thorough medical history is crucial. Key points include:
 - Recurrent episodes of wheezing, shortness of breath, chest tightness, and cough, particularly at night or early morning.
 - Symptoms that vary over time and in intensity.
 - Triggers such as allergens, exercise, cold air, and respiratory infections.
 - Personal or family history of asthma, allergies, or atopic conditions.
2. **Physical Examination:** While the physical exam may be normal between episodes, it is important to look for:
 - Wheezing on lung examination.
 - Signs of atopic conditions (e.g., eczema, allergic rhinitis).
 - Increased respiratory rate and use of accessory muscles during exacerbations.

Pulmonary Function Testing

1. **Spirometry:** This is the preferred method to confirm the diagnosis. Key spirometric criteria include:
 - Reduced FEV1 (forced expiratory volume in one second).
 - FEV1/FVC (forced vital capacity) ratio below the lower limit of normal.
 - Significant reversibility of airway obstruction (an increase in FEV1 of $\geq 12\%$ and 200 mL after bronchodilator administration).
2. **Peak Expiratory Flow (PEF):** PEF monitoring can be useful for assessing

variability in airflow obstruction. A day to night variation of more than 10% suggests asthma.

3. Additional Tests: In some cases, further tests such as bronchial provocation testing or measurement of exhaled nitric oxide (FeNO) may be needed.

Differential Diagnosis

It is essential to consider and rule out other conditions that can mimic asthma, such as chronic obstructive pulmonary disease (COPD), vocal cord dysfunction, heart failure, and respiratory infections.

Pharmacological Therapy

Medications play a vital role in managing asthma, aiming to relieve symptoms, improve lung function, and prevent exacerbations. Treatment regimens are often tailored to the severity of asthma and the individual patient's needs. Knowing the medications recommended to treat asthma ensures your management is appropriate.

1. Bronchodilators

- Short-acting beta2-agonists (SABAs): Medications such as albuterol are used for immediate symptom relief. These medications are being replaced by LABAs due to better outcomes and fewer side effects.

- Long-acting beta2-agonists (LABAs) and long-acting muscarinic antagonists (LAMAs): LABAs (long-acting beta2-agonists) like salmeterol, formoterol, and vilanterol, and LAMAs (long-acting muscarinic antagonists) like glycopyrrolate and umeclidinium are used for maintenance therapy to provide prolonged symptom control.

2. Inhaled Corticosteroids (ICS)

- Recommended for patients with a history of persistent symptoms despite bronchodilator therapy.

- ICS such as budesonide and fluticasone can reduce inflammation and are often used in combination with LABAs (ICS+LABA) or LAMAs (ICS+LABA+LAMA) for better control. Combination inhalers (ICS + LABA/ICS + LABA + LAMA) provide both anti-inflammatory and bronchodilating effects.

3. Biologics

- Biologics are essentially anti-bodies that work by targeting key molecules involved in the inflammatory process. These medications work by blocking IgE (Immunoglobulin E), certain Interleukin cytokines, or both. IgE is involved in allergic type reactions, while Interleukin cytokines increase eosinophils, a type of white blood cell involved in inflammation.

Management of Asthma

The management of asthma is guided by the goals of achieving good symptom control and minimizing the risk of exacerbations, decline in lung function, and treatment-related side effects. The GINA guidelines emphasize a stepwise approach to asthma management, and the AAAAI provides additional recommendations to optimize patient care.

Stepwise Management Approach

1. Step 1: Intermittent Asthma

- Preferred: Low-dose ICS+formoterol (Symbicort) as needed. ICS+albuterol is an alternative. The Global Initiative for Asthma recommendations are based on both the reduction in exacerbation risk with ICS+formoterol and ICS+albuterol reliever therapies compared with SABA reliever (albuterol) therapy and the well-established risks of SABA reliever therapy.

2. Step 2: Mild Persistent Asthma

- Preferred: Daily low-dose inhaled corticosteroid (ICS) or as-needed low-dose ICS+formoterol (Symbicort).

3. Step 3: Moderate Persistent Asthma

- Preferred: Low-dose ICS+LABA (Breo, Dulera, Symbicort, Advair).

4. Step 4: Severe Persistent Asthma

- Preferred: Medium-dose ICS+LABA (Breo, Dulera, Symbicort, Advair). An ICS+LABA+LAMA (Trelegy) is an alternative.

5. Step 5: Difficult-to-Control Asthma

- Consider high-dose ICS+LABA or ICS+LABA+LAMA (Trelegy) and referral to a specialist.
- Consider adding a biologic medication, such as anti-IgE, anti-IL5, anti-IL4/IL13 medication, or anti-TSLP therapy.

Biologic Treatments

Biologic treatments have emerged as a promising option, offering new hope for those with difficult-to-control asthma. Biologic treatments are a class of drugs derived from the cells of living organisms or contain components of living organisms. These drugs are often monoclonal antibodies (mAb), giving rise to drug names ending in -mab. They target specific pathways in the immune system that contribute to the inflammation and hyper-responsiveness characteristic of

asthma. Unlike traditional medications that provide broad-based relief, biologics are designed to intervene at specific points in the inflammatory cascade, thereby offering more targeted and effective control of the disease.

Mechanism of Action

Asthma is a heterogeneous disease, meaning its underlying mechanisms can vary significantly among patients. Biologics work by targeting key molecules involved in the inflammatory process. These targets may be small inflammatory proteins (cytokines) called Interleukin, or white blood cells called eosinophils, which produce Interleukins and are not normally found in healthy lung tissue. These targets include:

1. IgE (Immunoglobulin E): Elevated levels of IgE are associated with allergic asthma. Omalizumab (Xolair) is an anti-IgE monoclonal antibody that binds to IgE, preventing it from triggering allergic reactions. IgE levels are determined by blood testing.
2. IL-5 (Interleukin-5): IL-5 is a cytokine that plays a critical role in the growth, activation, and survival of eosinophils, a type of white blood cell involved in asthma. Mepolizumab (Nucala), reslizumab (Cinqair), and benralizumab (Fasenra) are anti-IL-5 biologics that reduce eosinophil levels and inflammation. Eosinophils levels are determined by blood testing.
3. IL-4 and IL-13: These cytokines are involved in the inflammatory response in asthma. Dupilumab (Dupixent) is an anti-IL-4/IL-13 monoclonal antibody that blocks IL-4R receptors and decreases signaling pathways of both cytokines and eosinophils, reducing inflammation and improving lung function.
4. Human thymic stromal lymphopoietin (TSLP): Tezepelumab-ekko (Tezspire) is a monoclonal anti-TSLP antibody that reduces cells and cytokines associated with inflammation and reduced lung function, including blood eosinophils, airway submucosal eosinophils, IgE, IL-5, and IL-13.

Indications and Benefits

Biologics are primarily indicated for patients with moderate to severe asthma who do not respond adequately to standard treatments. They are particularly beneficial for:

- Eosinophilic Asthma: Patients with high levels of eosinophils in their blood or sputum often respond well to anti-IL-5, anti-IL4/13, and anti-TSLP therapies.
- Allergic Asthma: Omalizumab and Tezepelumab-ekko are effective for patients with elevated IgE levels and sensitivity to perennial allergens.

- Oral Corticosteroid-Dependent Asthma: Biologics can reduce the need for oral corticosteroids, thereby minimizing the associated side effects.

Clinical trials have demonstrated that biologics can significantly reduce asthma exacerbations, improve lung function, and enhance the overall quality of life. Patients often experience fewer symptoms, reduced need for rescue medications, and decreased hospitalizations and emergency room visits.

Administration and Safety

Biologic treatments for asthma are typically administered via subcutaneous injection or intravenous infusion. The frequency of administration varies depending on the specific biologic, ranging from bi-weekly to monthly injections.

While biologics are generally well-tolerated, potential side effects include injection site reactions, headaches, and, in rare cases, allergic reactions. Long-term safety data are still being collected, but current evidence suggests that biologics are a safe and effective option for appropriate patients.

Non-Pharmacological Interventions

1. Trigger Avoidance: Identifying and avoiding triggers (e.g., allergens, smoke, pollution) is essential. The AAAAI emphasizes the importance of environmental control measures, including using air purifiers, avoiding indoor smoking, and managing dust mites.
2. Patient Education: Educating patients about asthma, proper inhaler technique, and the importance of adherence to treatment. The AAAAI recommends using educational materials and asthma action plans tailored to the patient's literacy level and cultural background.
3. Asthma Action Plan: Developing a personalized action plan that outlines daily management and how to handle worsening symptoms.

Special Considerations

1. Severe Asthma: Referral to a specialist for further evaluation and consideration of advanced therapies, such as biologics and/or bronchial thermoplasty. The AAAAI highlights the role of comprehensive asthma care centers in managing severe cases.
2. Comorbidities: Addressing comorbid conditions (e.g., obesity, GERD, rhinitis) that can impact asthma control.
3. Pregnancy: Managing asthma in pregnant women requires careful consideration to balance maternal and fetal health. The AAAAI advises close monitoring and adjustment of medications to maintain optimal control.

Monitoring and Follow-Up

Regular follow-up is crucial to assess control, adjust treatment, and address any concerns. Key points include:

- Asthma Control Assessment: Using tools such as the Asthma Control Test (ACT) found at asthma.com to monitor symptom control.
- Lung Function Testing: Periodic spirometry to monitor lung function.
- Adherence and Technique: Ensuring correct inhaler technique and adherence to prescribed treatment. All patients benefit from having a peak flow meter and an asthma action plan.

Asthma Action Plan

An asthma action plan is a personalized strategy developed in collaboration with your healthcare provider to manage asthma effectively. It includes guidance on daily management and how to handle worsening symptoms or asthma attacks. Below are the basic elements of an asthma action plan:

Green Zone: Doing Well

- Symptoms: No cough, wheeze, chest tightness, or shortness of breath during the day or night. Can do usual activities.
- Peak Flow: More than 80% of your personal best.
- Medications: Take your daily controller medicines as prescribed.
 - Controller Medicine and instructions
 - Reliever Medicine and instructions

Yellow Zone: Caution

- Symptoms: Cough, wheeze, chest tightness, or shortness of breath. Waking at night due to asthma. Can do some, but not all, usual activities.
- Peak Flow: 50-80% of your personal best.
- Medications:
 - Continue taking your daily controller medicines.
 - Add reliever medicine
 - If symptoms do not improve after one hour of reliever medicine, contact your healthcare provider.

Red Zone: Medical Alert

- Symptoms: Very short of breath. Quick-relief medicines have not helped. Cannot

do usual activities. Symptoms are the same or get worse after 24 hours in the yellow zone.

- Peak Flow: Less than 50% of your personal best.
- Medications:
 - Take your reliever medicine right away
 - Call your healthcare provider or go to the emergency room immediately.
 - If you cannot reach your healthcare provider, call 911 or an emergency medical service.

Emergency Contact Information

- Healthcare Provider
- Emergency Contact

Additional Instructions

- Trigger Avoidance: List your known triggers and steps to avoid them.
- Exercise: Instructions on how to manage asthma during physical activity.

Note: Regularly review and update your asthma action plan with your healthcare provider to ensure it reflects your current condition and treatment.

ASTHMA ACTION PLAN

For: _____ Doctor: _____ Date: _____

Doctor's Phone Number: _____ Hospital/Emergency Department Phone Number: _____

GREEN ZONE			
DOING WELL	Daily Medications	How much to take	When to take it
<ul style="list-style-type: none"> No cough, wheeze, chest tightness, or shortness of breath during the day or night Can do usual activities <p>And, if a peak flow meter is used, Peak flow: more than _____ (80 percent or more of my best peak flow) My best peak flow is: _____</p>	_____ _____ _____ _____	_____ _____ _____ _____	_____ _____ _____ _____
Before exercise	<input type="checkbox"/> _____	<input type="checkbox"/> 2 or <input type="checkbox"/> 4 puffs	5 minutes before exercise
YELLOW ZONE			
ASTHMA IS GETTING WORSE <ul style="list-style-type: none"> Cough, wheeze, chest tightness, or shortness of breath, or Waking at night due to asthma, or Can do some, but not all, usual activities <p>Peak flow: _____ to _____ (50 to 79 percent of my best peak flow)</p>	1st → Add: quick-relief medicine—and keep taking your GREEN ZONE medicine. _____ (quick-relief medicine)	_____ Number of puffs or <input type="checkbox"/> Nebulizer, once	Can repeat every _____ minutes up to maximum of _____ doses
<p>2nd → If your symptoms (and peak flow, if used) return to GREEN ZONE after 1 hour of above treatment:</p> <input type="checkbox"/> Continue monitoring to be sure you stay in the green zone.	<p>–Or–</p> <p>If your symptoms (and peak flow, if used) do not return to GREEN ZONE after 1 hour of above treatment:</p> <input type="checkbox"/> Take: _____ (quick-relief medicine)	_____ Number of puffs or <input type="checkbox"/> Nebulizer	
<p>–Or–</p> <input type="checkbox"/> Add: _____ mg per day For _____ (3-10) days (oral steroid) <input type="checkbox"/> Call the doctor <input type="checkbox"/> before/ <input type="checkbox"/> within _____ hours after taking the oral steroid.			
RED ZONE			
MEDICAL ALERT! <ul style="list-style-type: none"> Very short of breath, or Quick-relief medicines have not helped, Cannot do usual activities, or Symptoms are same or get worse after 24 hours in Yellow Zone <p>Peak flow: less than _____ (50 percent of my best peak flow)</p>	Take this medicine: <input type="checkbox"/> _____ (quick-relief medicine)	_____ Number of puffs or <input type="checkbox"/> Nebulizer	
<p>–Or–</p> <input type="checkbox"/> _____ mg (oral steroid)	Then call your doctor NOW. Go to the hospital or call an ambulance if: <ul style="list-style-type: none"> You are still in the red zone after 15 minutes AND You have not reached your doctor. 		
DANGER SIGNS <ul style="list-style-type: none"> Trouble walking and talking due to shortness of breath Lips or fingernails are blue 	→ Take _____ puffs of _____ (quick relief medicine) AND Go to the hospital or call for an ambulance _____ (phone) NOW!		

See the reverse side for things you can do to avoid your asthma triggers.

Conclusion

The GINA guidelines and AAAAI recommendations provide a comprehensive framework for the diagnosis and management of asthma, emphasizing the importance of a personalized and stepwise approach based upon severity of asthma, treatment response and levels of IgE and eosinophils. By following these guidelines, healthcare providers can help patients achieve better asthma control, reduce exacerbations, and improve their quality of life.

Asthma and COPD Medicines

Quick Reliever Medicines

Short-Acting Beta₂-Agonists (SABA)

Albuterol Sulfate HFA Albuterol sulfate 90 mcg	Albuterol Sulfate Neb Albuterol sulfate 2.5 mg/3 mL	ProAir[®] Digihaler[®] Albuterol sulfate 177 mcg	ProAir[®] RespiClick[®] Albuterol sulfate 177 mcg	Proventil[®] HFA Albuterol sulfate 125 mcg	Ventolin[®] HFA Albuterol sulfate 90 mcg	Xopenex HFA[®] Levalbuterol tartrate 2.5 mcg	Xopenex[®] Neb Levalbuterol hydrochloride 2.0 mg/3 mL, 0.63 mg/2 mL, 1.25 mg/2 mL
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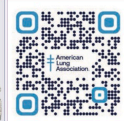
Short-Acting Muscarinic Antagonists (SAMA)

Atrovent[®] HFA Ipratropium bromide 17 mcg	Atrovent[®] Neb Ipratropium bromide 250/500 mcg
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Short-Acting Combinations (SABA-SAMA)

Combivent[®] RespiMat[®] Ipratropium bromide and albuterol 2.5 mg/3 mg/2 mL	Combivent[®] RespiClick[®] Ipratropium bromide and albuterol 2.5 mg/3 mg/2 mL
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How-To Videos



Maintenance/Controller Medicines

Inhaled Corticosteroids (ICS) asthma only

Avsco[®] HFA Fluticasone 45/90 mcg	ArmonAir[®] RespiClick[®] Fluticasone propionate 250/125/250 mcg	Arnuity[®] Ellipta[®] Fluticasone furoate 100/200 mcg	Asmanex[®] HFA Mometasone furoate 100/200 mcg	Asmanex[®] Twisthaler[®] Mometasone furoate 110/220 mcg	Budesonide Inhalation Suspension Budesonide 0.25 mg/2 mL, 0.5 mg/2 mL, 1 mg/2 mL	Flovent[®] Diskus[®] Fluticasone propionate 50/100/200 mcg	Flovent[®] HFA Fluticasone propionate 44/110/220 mcg	Pulmicort[®] Flexhaler[®] Budesonide 90/180 mcg	Pulmicort RespiPuls[®] Budesonide inhalation suspension 2.25 mg/2 mL, 0.5 mg/2 mL	QVAR[®] Redihaler[®] Beclomethasone dipropionate 42/84 mcg
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Combination Therapy (Inhaled Corticosteroid - Long-Acting Beta₂-Agonists) (ICS-LABA)

Advair Diskus[®] Fluticasone propionate and salmeterol 100/50, 200/50, 300/50 mcg	Advair HFA Fluticasone propionate and salmeterol 40/21, 110/21, 220/21 mcg	AirDuo[®] RespiClick[®] Fluticasone propionate and salmeterol 55/14, 113/14, 220/14 mcg	Breo[®] Ellipta[®] Fluticasone and vilanterol 100/25, 200/25 mcg	Symbicort[®] Budesonide and formoterol fumarate dihydrate 80/4.5, 160/4.5 mcg	Dulera[®] Mometasone furoate and formoterol fumarate dihydrate 200, 100/5, 200/5 mcg	Wixela[®] Inhub[®] Fluticasone propionate and salmeterol xinafoate 100/50, 200/50, 300/50 mcg
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Triple Therapy (ICS-LABA-LAMA)

Trelegy Ellipta[®] Fluticasone, vilanterol, and umeclidinium 100 mg/25.2 mg/25.2 mg	Bretri Aerosphere[®] Budesonide, glycopyrronium bromide, and formoterol fumarate dihydrate 160/9/4 mcg
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Long-Acting Muscarinic Antagonists (LAMA)

Increase[®] Ellipta[®] Aclidinium bromide 80.5 mcg	Lonhala Magnair[®] Glycopyrronium 25 mg/2 mL	Spiriva[®] Handihaler[®] Tiotropium bromide 18 mcg	Spiriva[®] RespiMat[®] Tiotropium bromide 1.25 mg	Tudorza[®] Pressair[®] Umeclidinium bromide 405 mcg	Yupelri[®] Neb Umeclidinium bromide 175 mg/2 mL
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Long-Acting Beta₂-Agonists (LABA) COPD only

Brovana[®] Neb Formoterol fumarate dihydrate 65 mcg	Perforomist[®] Neb Formoterol fumarate dihydrate 20 mcg	Serevent[®] Diskus[®] Salmeterol xinafoate 50 mcg	Striverdi[®] RespiMat[®] Vilanterol and umeclidinium bromide/hydrochloride 23 mcg
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LAMA-LABA COPD only

Anoro[®] Ellipta[®] Fluticasone, vilanterol, and umeclidinium 50/22.5/22.5 mcg	Brevo[®] Aerosphere[®] Budesonide, glycopyrronium bromide, and formoterol fumarate dihydrate 94/8 mcg	Duaklir[®] Pressair[®] Umeclidinium bromide and formoterol fumarate dihydrate 40/12 mcg	Siloato[®] RespiMat[®] Umeclidinium bromide and vilanterol fumarate dihydrate 2.5/2.5 mcg
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Add-On Medicines

Monoclonal Antibody (biologics, injection)	PDE4 Inhibitor	Leukotriene Receptor Antagonists (LTRA)
Cincal[®] mepolizumab 100 mg	Daliresp[®] roflumetast 250/500 mg	Singular[®] montelukast sodium 45/90 mg
Duixent[®] dupilumab 300/600 mg	Fasenra[®] sulfasalazine 30 mg	Zyflo[®] zileuton 360/720 mg
Nucala[®] mepolizumab 100 mg	Tezspire[®] roflumetast 250 mg	Xolair[®] omalizumab 75/150 mg

Use a valved holding chamber/spacer

All HFA inhalers should be used with a compatible valved holding chamber/spacer.

Definitions

- ICS = Inhaled Corticosteroid
- ICS-LABA or LAMA-LABA = Combination Therapy
- ICS-LABA-LAMA = Triple Therapy
- LABA = Long-Acting Beta₂-Agonist
- LAMA = Long-Acting Muscarinic Antagonist
- LTRA = Leukotriene Receptor Antagonist
- SABA = Short-Acting Beta₂-Agonist
- SAMA = Short-Acting Muscarinic Antagonist
- SMART = Single Maintenance and Reliever Therapy

Disease States: **A** Asthma **C** COPD **G** Generic **S** SMART Therapy

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SMART

SMART (Single Maintenance And Reliever Therapy) is a next-generation asthma treatment containing an ICS (inhaled corticosteroid) with formoterol (long-acting beta agonist) combined into one inhaler. SMART includes formoterol due to its ability to be fast-acting for rapid onset of asthma symptoms (similar to a short-acting beta agonist) with a longer lasting effect. This SMART treatment option may be prescribed to those with moderate to severe persistent asthma, as a daily controller medication (ICS/ formoterol) and/or to treat rapid onset of symptoms as a quick-relief medicine.

Key Messages

- Less complicated to use (one single inhaler) for managing asthma symptoms and just as effective
- Used to treat symptoms when they start and also for daily maintenance
- Always recommend use of MDI with a valved holding chamber/spacer
- This treatment option is not available for everyone. If someone is already well controlled on current treatment, shared decision making is important before making changes.
- Rinse mouth and spit out after use
- Talk to your healthcare provider for more information

Resources for Asthma and COPD

- Asthma Care Quick Reference**
https://www.nhlbi.nih.gov/files/docs/guidelines/asthma_qrg.pdf
- GOLD Reports for COPD**
www.goldcopd.org
- American Lung Association**
www.lung.org/asthma www.lung.org/COPD

How to use a metered-dose inhaler with a valved holding chamber (spacer)

Prime a brand-new inhaler: Before using it for the first time, if you have not used it for more than 7 days, or if it has been dropped.

- Shake inhaler 10 seconds.
- Take the cap off the inhaler and valved holding chamber. Make sure the mouthpiece and valved holding chamber are clean and there is nothing inside the mouthpieces.
- Put inhaler into the chamber/spacer.
- Breathe out away from the device.
- Put chamber mouthpiece in mouth.
- Press inhaler once and breathe in deep and steadily.
- Hold your breath for 10 seconds, then breathe out slowly.
If you need another puff of medicine, wait 1 minute and repeat steps 4-7.
- Rinse with water and spit it out.

Proper inhalation technique is important when taking your asthma medicine(s) and monitoring your breathing. Make sure to bring all your medicines and devices to each visit with your primary care provider or pharmacist to check for correct use, or if you have trouble using them.

For more videos, handouts, tutorials and resources, visit Lung.org.

Scan the QR Code to access How-To Videos



You can also connect with a respiratory therapist for one-on-one, free support from the American Lung Association's Lung HelpLine at 1-800-LUNGUSA.