Management of Asthma in the Elderly including Management of Asthma-COPD Overlap Syndrome

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Asthma in Special Populations
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Management of Asthma in the Elderly including Management of Asthma-COPD Overlap Syndrome

- Describe special characteristics, management, and treatment strategies of asthma in the elderly.
- Discuss clinical similarities and differences between asthma and chronic obstructive pulmonary disease (COPD).
- Evaluate interventions to improve asthma control and decrease asthma burden in elderly patients with asthma.
Asthma is a heterogeneous disease with significant variability in disease expression, severity, and response to therapeutic measures\(^1\)

Asthma in the elderly is a heterogeneous disease as prevalent as in the youngest population (5% to 10%) and affecting more often women\(^1\)

Older adults with asthma have an increased likelihood of comorbidities and polypharmacy, with possible worsening of asthma control and reduced treatment adherence\(^2,3\)

Special Characteristics of Asthma in the Elderly

- Lung function decreases with age
- Stiffening of the chest wall, reduced respiratory muscle function, and an increase in residual volume from loss of elastic recoil
- Elderly patients with asthma have reduced response to bronchodilators and glucocorticoids
- Naive T cells decrease, memory T cells increase, and B-cell function decreases, but there is a lesser decrease in innate immunity
- Eosinophil function remains the same, but neutrophil numbers increase

Characteristics of Asthma in the Elderly

- **Epidemiological**
  - Increased morbidity and mortality
  - Less frequent atopy

- **Clinical**
  - Underdiagnosed and undertreated
  - Asthma control more difficult to achieve
  - Reduced perception of symptoms
  - Difficulties to perform pulmonary function tests
  - Numerous co-morbidities

- **Pathophysiology**
  - Mixed (more neutrophilic airway inflammation)
  - More severe airway obstruction
  - Loss of lung elastic recoil - reduced respiratory muscles strength - small airways involvement
  - Systemic inflammation and immunosenescence

- **Management problems**
  - Insufficient understanding of the disease
  - Memory impairment, hearing loss, poor sight
  - Psycho-socioeconomic problems

- **Therapy**
  - Poor adhesion to therapy and follow-up
  - Poor inhaler technique
  - Polypharmacy and increased risk of interactions

- **General**
  - Poor nutrition, sedentary, weight gain
  - Reduced access to care

Establishing a Diagnosis of Asthma

To establish a diagnosis of asthma, the clinician should determine:
1. episodic symptoms of airflow obstruction or airway hyper-responsiveness are present
2. airflow obstruction is at least partially reversible
3. alternate diagnoses are excluded

Guideline recommended methods to establish the diagnosis:
1. detailed medical history
2. a physical examination focusing on the upper respiratory tract, chest, and skin
3. spirometry to demonstrate obstruction and assess reversibility

Diagnosis should include chest radiography and computed tomographic scanning to diagnose other lung diseases if FEV1 remains low after treatment

Reversibility is determined by an increase in FEV1 of 12% or greater from the baseline value or by an increase of 10% or greater of predicted FEV1 after inhalation of a short-acting bronchodilator

Asthma in the Elderly

Management is challenged by multiple factors:

- Misdiagnosis
- Underdiagnosis
- Undertreatment
- Comorbidities
- Potentially lower drug response

Current guidelines for asthma therapeutic management do not consider asthma in the elderly as a specific condition.
Diagnostic and Treatment Comparison of Elderly and Younger Patients with Asthma

<table>
<thead>
<tr>
<th>Test/Characteristic</th>
<th>Elderly</th>
<th>Young</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spirometry</td>
<td>May be less useful in frail patients; reference standards not widely available</td>
<td>Generally useful tool to assess asthma severity</td>
</tr>
<tr>
<td>Bronchodilator responsiveness eNO</td>
<td>May be less pronounced May be useful</td>
<td>Variable but generally greater May be useful</td>
</tr>
<tr>
<td>Methacholine challenge</td>
<td>Less often used because of more frequent contraindications (e.g., cardiovascular disease)</td>
<td>Useful; overall fewer contraindications</td>
</tr>
<tr>
<td>Atopy</td>
<td>Less common</td>
<td>Common</td>
</tr>
<tr>
<td>Comorbidities</td>
<td>COPD, heart disease more common</td>
<td>Allergic rhinitis more common</td>
</tr>
<tr>
<td>Phenotypes</td>
<td>Limited knowledge, but late-onset asthma, long-standing asthma, and ACOS described</td>
<td>Multiple phenotypes described</td>
</tr>
<tr>
<td>Sputum cellularity</td>
<td>Generally more neutrophilin</td>
<td>Generally more eosinophilic</td>
</tr>
<tr>
<td>Therapy</td>
<td>No age-specific guidelines Optimal regimen unknown More susceptible to adverse effects due to comorbidities, drug-to-drug interactions, and polypharmacy Inability to use certain inhalers due to lack of dexterity and reduced inspiratory flow</td>
<td>Guideline-specific regimens in place that address the needs of most patients</td>
</tr>
</tbody>
</table>

Definition of abbreviations: ACOS = asthma–COPD overlap syndrome; COPD = chronic obstructive pulmonary disease; eNO = exhaled nitric oxide.
Asthma in the Elderly: Co-morbidities

- Asthma exacerbations and associated comorbidities contribute to the overall severity of the disease in elderly patients\(^1\)
- Comorbidities are considered key characteristics of geriatric patients and contribute to the clinical complexity of the elderly\(^2\)
- Contribute to poor asthma management outcomes compared to younger patients with asthma\(^3\)
- Differential diagnoses or comorbidities, such as chronic obstructive pulmonary disease (COPD) and congestive heart failure, may mask the diagnosis of asthma in these population\(^4\)
- Multiple studies have demonstrated that asthma is associated with depression, and that more severe asthma is associated with a greater risk and severity of depression\(^5\)

Pharmacologic Treatment
Pharmacologic Treatment

- Asthma tends to be more severe and is associated with a high morbidity and increased mortality in the elderly patient
- Treatment must be carefully selected and closely monitored
- Pharmacologic treatment must be adjusted to achieve and maintain control and is basically the same for all ages
  - elderly patients have reduced response to bronchodilators and increased side effects from short acting beta agonist and glucocorticoids

Asthma in the Elderly: Pharmacological Management

Short-acting Beta agonists (SABA) and Long-acting Beta agonists (LABA)

- SABAs should be provided as rescue therapy, on demand, at the minimal dose and frequency.
- SABAs are usually well tolerated but if they cause tremor or tachycardia, the dose should be reduced while maintenance therapy revised to minimize their need.
- Long-acting β-adrenergic agonist can have cardiotoxic effects in patients with heart disease. Aerosol anticholinergic agents can be an alternative. Both increase the anti-inflammatory effects of glucocorticoids.
- SABAs should not be utilized more than 2-3 times a week.
- LABAs should never be used alone as long-term regular monotherapy for asthma.

Short-acting Beta agonists (SABA) and Long-acting Beta agonists (LABA)

Theoretically, older patients may have a reduced response to bronchodilators as a result of age-related changes such as stiffening of the chest wall, reduced respiratory muscle function, and an increase in residual volume from loss of elastic recoil in the lung.\(^1,2\)

Data have revealed that albuterol is effective in both younger and older patients, and the addition of the LABA salmeterol to the ICS fluticasone has been reported to decrease the risk of asthma-related serious exacerbations compared with fluticasone alone.\(^2\)

Inhaled Corticosteroids (ICS)

- ICS are the mainstay of asthma treatment in the elderly, although they are at times insufficiently used in this population\(^1,3\)

- Asthmatic phenotypes characterized by neutrophilic inflammation of the airways are less likely to respond to ICS than those with prevalent eosinophilic inflammation\(^2\)

- In the elderly patient with asthma neutrophilic airway inflammation is more common than in previous ages\(^3\)


Leukotriene Receptor Antagonists (LTRA)

- Cysteiny1 leukotrienes (cysLTs, TC4, LTD4, and LTE4) are potent bronchoconstrictors and chemoattractant for eosinophils → an important therapeutic targets in patients with asthma

- Antagonize cysLT1 receptor

- LTRAs antagonize cysLT1 receptor

- Alternative treatment to ICS and LABA in the elderly

- May contribute to improving adherence profile

- May increase safety of asthma therapy by avoiding ICS and LABA side-effects, which are more frequent in the elderly

- As add-on therapy to ICS, LTRA appears to have a modest steroid-sparing effect among symptomatic patients


2. Chauhan BF, Ducharme FM. Anti-leukotriene agents compared to inhaled corticosteroids in the management of recurrent and/or chronic asthma in adults and children. Cochrane Database Syst Rev. 2012;5:CD002314
Anticholinergics

- Most commonly used short-acting anticholinergic → not a first-choice as a reliever, being less effective than β2-agonists
- Some elderly patients have a particularly good response to anticholinergics
- Tiotropium may ameliorate chronic asthmatic cough by modulating capsaicin cough reflex sensitivity, possibly providing a new therapeutic option for treating refractory cough in patients with asthma

Long-acting muscarinic antagonist (LAMA): Tiotropium

- Tiotropium is a long-acting muscarinic antagonist (LAMA) with duration of action exceeding 24 hours-- attributed to its slow dissociation from muscarinic receptors.

- LAMAs have the potential to improve asthma control include bronchodilation or inhibition of cholinergically mediated bronchoconstriction, possibly inhibit airway smooth muscle hypertrophy and hyperresponsiveness\(^1,2\)

- Tiotropium has been included as a new add-on treatment for GINA Steps 4 and 5 in patients aged \(\geq\) 18 years with a history of exacerbations (Evidence A)\(^3\)


Oral Corticosteroids

- Recommended as step 5 management in the GINA guidelines\(^1\)

- Associated with many side effects\(^2\)
  
  osteoporosis, fracture, infection, obesity, coronary artery disease, avascular necrosis, stroke, cataract, diabetes and skin thinning, in a dose-dependent way, which could be more problematic in severe or elderly asthma patients

- Limited to patients who could have more benefits than side effects

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Biologic Agents

- Studies and reviews have found that omalizumab is an effective and safe therapy option for moderate to severe allergic asthma. Anti-IgE Trials of older adult patients with severe allergic asthma, omalizumab had significant clinical benefit\(^1\),\(^4\).
- Anti-IL-5 therapy with mepolizumab, reslizumab, and benralizumab has been shown, in phase III trials to be efficacious in reducing asthma attacks and improving lung function in poorly controlled patients with asthma\(^2\),\(^3\).
- Subgroup analysis from recent trial data has suggested that mepolizumab is effective in elderly asthmatics with eosinophilic inflammation\(^4\).
- Data are still lacking in severe "nonatopic" asthma in the elderly.
- Anti-IL-4 Ralpha (dupilumab), anti-IL-13 (tralokinumab), and other targeted therapies hold promise as potential future targeted therapies in asthma\(^2\),\(^3\).
- GINA 2018 Step 5 recommends anti-IgE or anti IL5 add-on treatment\(^5\).

Other Treatments

- **Theophylline**: used as oral sustained-release formulations
  - third-choice, but may provide a benefit as add-on therapy in patients who do not achieve control with ICS/LABAs
  - Relatively small therapeutic index with significant side effects, particularly at higher doses and in the elderly

- Long-term use of macrolides is gaining popularity in neutrophilic forms of difficult-to-treat asthma

**Theophylline is now rarely used, but if prescribed close monitoring is imperative due to potential for side-effects and risk of drug interactions, particularly in the aged patient, with frequent heart conditions and poly-pharmacy**


# Adverse Effects Non-Asthma Medications

<table>
<thead>
<tr>
<th>Medication</th>
<th>Adverse Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beta-blocker</td>
<td>Bronchospasm</td>
</tr>
<tr>
<td></td>
<td>Diminished response to bronchodilator</td>
</tr>
<tr>
<td></td>
<td>Worsening asthma</td>
</tr>
<tr>
<td>NSAID</td>
<td>Bronchospasm</td>
</tr>
<tr>
<td></td>
<td>Worsening asthma</td>
</tr>
<tr>
<td>ACE-I</td>
<td>Increased cough</td>
</tr>
<tr>
<td>Non-potassium-sparing diuretics</td>
<td>Worsening cardiac function</td>
</tr>
<tr>
<td></td>
<td>hypokalemia</td>
</tr>
<tr>
<td>Cholinergic agents</td>
<td>Bronchospasm</td>
</tr>
</tbody>
</table>

Pharmacological Challenges in the Treatment of Asthma in the Elderly

- Polypharmacotherapy is a significant risk factor for adverse drug reactions in the elderly

- Concomitant non-respiratory medications

- Pharmacokinetic changes that are primarily due to the decline in the function of the liver and the kidneys and reduced hepatic clearance of drugs increases the potential for drug interactions

- Lack of coordination between activation of the device and inhalation of the active drug may increase the oral deposition and decrease the lung deposition

- Long-term and high-dose use of ICS may be associated with increased risk of adverse events

- Bronchodilators are affected by ageing-related changes of their pharmacokinetic and pharmacodynamic properties

- Anticholinergic response is decreased in parasympathetic activity and reduction in receptor numbers or post-receptor coupling with age


Clinical Similarities and Difference: Asthma and Chronic Obstructive Pulmonary Disease

### Table 1 Features favoring asthma or COPD for syndromic diagnosis of airway disease based on the Global Initiative for Asthma/Global Initiative for Chronic Obstructive Lung Disease report

<table>
<thead>
<tr>
<th>Feature</th>
<th>Asthma</th>
<th>COPD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age of onset</td>
<td>Before age 20 years</td>
<td>After age 40 years</td>
</tr>
<tr>
<td>Pattern of respiratory</td>
<td>Variation in symptoms over time</td>
<td>Persistence of symptoms despite treatment</td>
</tr>
<tr>
<td>symptoms</td>
<td>Symptoms worsen during the night or early</td>
<td>Good and bad days but always daily</td>
</tr>
<tr>
<td></td>
<td>morning</td>
<td>respiratory symptoms and exertional dyspnea</td>
</tr>
<tr>
<td></td>
<td>Symptoms triggered by exercise, emotional</td>
<td>Chronic cough and sputum preceded by</td>
</tr>
<tr>
<td></td>
<td>change (including laughter), or exposure to</td>
<td>onset of dyspnea, unrelated to triggers</td>
</tr>
<tr>
<td></td>
<td>dust/allergens</td>
<td>Record of persistent airflow limitation</td>
</tr>
<tr>
<td>Lung function</td>
<td>Record of variable airflow limitation (spirometry, peak flow)</td>
<td>(post-bronchodilator FEV/FVC &lt;0.7) Abnormal</td>
</tr>
<tr>
<td>Lung function between symptoms</td>
<td>Normal</td>
<td>Previous doctor diagnosis of asthma</td>
</tr>
<tr>
<td>Past history or family</td>
<td>Previous doctor diagnosis of asthma</td>
<td>Previous doctor diagnosis of COPD, chronic</td>
</tr>
<tr>
<td>history</td>
<td></td>
<td>bronchitis, or emphysema</td>
</tr>
<tr>
<td></td>
<td>Family history of asthma and other allergic</td>
<td>Heavy exposure to a risk factor: tobacco</td>
</tr>
<tr>
<td></td>
<td>conditions (allergic rhinitis, dermatitis)</td>
<td>smoke and biomass fuels</td>
</tr>
<tr>
<td>Time course</td>
<td>No worsening of symptoms over time. Symptoms</td>
<td>Symptoms slowly worsen over time (progressive course over years)</td>
</tr>
<tr>
<td></td>
<td>vary either seasonally or from year to year</td>
<td>Rapid-acting bronchodilator treatment provides only limited symptom relief</td>
</tr>
<tr>
<td></td>
<td>May improve spontaneously or have a response</td>
<td></td>
</tr>
<tr>
<td></td>
<td>to bronchodilator immediately or to ICS over weeks</td>
<td></td>
</tr>
<tr>
<td>Chest X-ray</td>
<td>Normal</td>
<td>Severe hyperinflation</td>
</tr>
</tbody>
</table>

**Notes:** Adapted with permission from Global Initiative for Asthma and Global Initiative for Chronic Obstructive Lung Disease. Diagnosis of diseases of chronic airflow limitation: asthma, COPD, and asthma-COPD overlap syndrome (ACOS).\(^1\)

**Abbreviations:** FEV\(_1\), forced expiratory volume in 1 second; FVC, forced vital capacity; ICS, inhaled corticosteroid.

Asthma and COPD Overlap (ACO)

- Asthma and COPD also share several important clinical features, including cough and breathlessness, as well as many pathophysiologic mechanisms, including bronchoconstriction, airway inflammation, and excess mucous production. It is no surprise, thus, that patients with one diagnosis can often show signs consistent with the other.

- One of the strongest risk factors, outside of cigarette smoking, for the future development of COPD remains a diagnosis of childhood asthma, indicating that the link between these diseases is likely a lifelong phenomenon. As our population ages, a larger number of patients with obstructive airway disease will be classified as having overlap syndrome.

- Further study is certainly warranted at this time to establish diagnostic and therapeutic guidelines that are specifically tailored to this growing subset of patients.

- Realizing that the overlap syndrome may represent a distinct phenotype of asthma is important for the clinician and ongoing investigation is necessary to more fully define this group of patients and discover what treatments are most effective for them.
Patients with ACO Compared with COPD or Asthma

- Known to experience frequent exacerbations
- Have a poor quality of life
- More rapid decline in lung function
- Higher mortality
- Disproportionate amount of health care resources

Asthma and COPD Overlap

Zeki et al reported that 38% of elderly asthmatics corresponded with the overlap syndrome when it was defined as one of two clinical phenotypes:

1. allergic disease consistent with asthma (with or without emphysema or reduced DLco)

2. COPD with emphysema accompanied by reversible or partially reversible airflow obstruction (with or without an allergic syndrome or reduced DLco).

Suggesting an overlap syndrome of asthma and COPD was the most common situation in older patients

<table>
<thead>
<tr>
<th><strong>Asthma</strong></th>
<th><strong>COPD</strong></th>
<th><strong>Asthma-COPD overlap (ACO)</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Asthma is a heterogeneous disease, characterized by chronic airway inflammation. Defined by history of respiratory symptoms -- wheeze, shortness of breath, chest tightness and cough that vary over time and in intensity, together with variable expiratory airflow limitation.</td>
<td>COPD is a common, preventable and treatable disease that is characterized by persistent respiratory symptoms and airflow limitation due to airway and/or alveolar abnormalities caused by significant exposure to noxious particles or gases.</td>
<td>ACO is characterized by persistent airflow limitation with severe features, associated with asthma and several features usually associated with COPD. ACO identified by the features shared with asthma and COPD. This is not a definition, but a description for clinical use, as ACO includes several different clinical phenotypes and several different underlying mechanisms.</td>
</tr>
</tbody>
</table>

Interventions to Improve Asthma Control and Decrease Asthma Burden

- Management of asthma in elderly patients is directed at controlling symptoms and eliminating or reducing exacerbating triggers.
- Assess and monitor important exacerbating factors including comorbid diseases, appropriate medication usage, drug-drug interactions and drug side-effects, and physiologic differences.
- Consider long-acting muscarinic antagonist (LAMA) addition for patients with severe asthma.
- Manage osteoporosis and other coexisting diseases.
- Influenza and pneumococcal immunization.
Nonpharmacological Interventions

- Environmental controls
  
  Most common aeroallergens to which older patients are sensitized are not consistent among studies, but typically include cats, dust mites, and cockroaches\textsuperscript{1,2}

- Smoking cessation

- Influenza and pneumococcal vaccines

- Promotion of active healthy lifestyle, appropriate diet and exercise, appropriate weight

- Patient education and multidisciplinary management
  
  addressing various aspects of pharmacotherapy, education, psycho-socio-economical problems co-morbid conditions and acute care needs\textsuperscript{3}

\textsuperscript{1} King MJ, Bukantz SC, Phillips S, Mohapatra SS, Tamulis T, Lockey RF. Serum total IgE and specific IgE to Dermatophagoides pteronyssinus, but not eosinophil cationic protein, are more likely to be elevated in elderly asthmatic patients. Allergy Asthma Proc. 2004;25:321-325.


Management of Asthma in the Elderly: Questions We Must Address

What are the effects of aging on lung and immune system?
Better characterize the phenotype
  Role of microbiome and infections
  Role of environment
    Influence of atopy, smoking, co-morbidities, gender
Determine what is the optimal management of asthma
Should drug therapy be better targeted to this population
  What is the response to therapy?
  What are the risks?
How do we educate the elderly using shared decision-making and develop an effective multidisciplinary plan?

What other questions should we consider?
Summary

- Physiological changes and comorbidities impact the elderly patients diagnosis and management.
- Asthma is often underdiagnosed and undertreated in the elderly.
- Management of asthma in elderly patients is directed at controlling symptoms and eliminating or reducing exacerbating triggers.
- Assess and monitor important exacerbating factors including comorbid diseases, appropriate medication usage, drug-drug interactions and drug side-effects, and physiologic differences.
- Asthma management in older adults should include comprehensive asthma education and frequently monitoring symptoms and medications.
- Additional prospective studies with new biologic medications for asthma are needed in the aged population.