Overcome Asthma! Asthma in the elderly

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Elderly asthma: still we do not know much

- Introduction
  - High prevalence and morbidity
  - Pathophysiology
  - Clinical features

- Diagnostic challenges
- Therapeutic challenges
Elderly asthma: high prevalence

**Current asthma**: “current wheeze” by questionnaire plus methacholine AHR

Elderly asthma: high burden & mortality

<table>
<thead>
<tr>
<th></th>
<th>Elderly asthmatics (≥65 years)</th>
<th>Adult asthmatics (&lt;65 years)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mean±SD %</td>
<td>mean±SD %</td>
<td></td>
</tr>
<tr>
<td><strong>Hospital care</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inpatient</td>
<td>750±1.4 50</td>
<td>202±728 26</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Emergency services</td>
<td>60±75 4</td>
<td>51±98 7</td>
<td>0.533</td>
</tr>
<tr>
<td><strong>Care by physicians</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>General</td>
<td>37±28 2</td>
<td>24±28 3</td>
<td>0.004</td>
</tr>
<tr>
<td>Specialists</td>
<td>74±57 5</td>
<td>71±114 9</td>
<td>0.930</td>
</tr>
<tr>
<td>Medications</td>
<td>526±319 35</td>
<td>379±328 49</td>
<td>0.004</td>
</tr>
<tr>
<td>Diagnostic tests</td>
<td>43±18 4</td>
<td>46±19 6</td>
<td>0.731</td>
</tr>
<tr>
<td><strong>All direct costs</strong></td>
<td>1,490±1,444 100</td>
<td>773±832 100</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Vicente P et al. Respiration 2000

Impact of age on asthma outcomes

Older adults (>55 yrs) had higher mortality and morbidity than younger asthma patients (18-55 yrs).

Special characteristics of EA

- Great variability in the duration and severity of EA
- Onset can have been at any time since childhood but more often begins in middle age or later.
- Many have severe irreversible obstruction unrelated to the duration of the disease.
Age of onset: mostly after middle-ages

Elderly asthma cohort in Korea (2009-2010): current asthmatics referred to tertiary centers (n=1,000)
Previously, asthma was considered to be childhood-onset disease.

**Childhood-onset asthma**
- Atopy
- Genetic factor
- Perinatal environment
Changes in the paradigm

• Recently, a considerable proportion of adult asthma was found to be **late-onset disease**.

**Childhood-onset asthma**
- Atopy
- Genetic factor
- Perinatal environment

**Late-onset asthma (> 40 yrs)**
- What underlies the pathophysiology?
  : a motivation for paradigm change
Speculation: pathophysiology

Aging lung:
- ↓FEV1, FVC
- lung stiffening

Immunosenescence

Host & environmental factors:
- CRS, Smoking, obesity, microbial infection
Clinical characteristics of elderly asthma

Risk factors:
- Rhinosinusitis
- Smoking
- Obesity
- SE IgE

Elderly asthma: Late-onset (after age 50s)

Airway inflammation
- Eosinophilia (similar)
- More neutrophilia

Comorbid COPD
Small airway involvement

Lesser role:
- Atopy
- Genetic?
Staphylococcal enterotoxin IgE has close relationships with severe asthma in the elderly

Song WJ, Cho SH et al. In submission
Identification of 4 clusters in elderly asthma

Cluster 1: Longstanding asthma with marked airway obstruction

Cluster 2: Female predominant mild asthma

Cluster 3: Male predominant asthma with smoking history and airway obstruction

Cluster 4: Asthma associated with higher BMI and borderline lung functions

Park HW, Cho SH et al. ANAI 2014 In press
Cluster 1: exacerbation prone phenotype

The graph shows the percent of patients who did not experience an acute exacerbation over the months of follow-up, with different clusters indicated by different lines. The Log-rank P value is 0.01, indicating a statistically significant difference among the clusters.

Park HW, Cho SH et al. ANAI 2014 In press
Predictors for exacerbation in the elderly

<table>
<thead>
<tr>
<th>Factor</th>
<th>Adjusted Relative Risk</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (male vs female)</td>
<td>1.13</td>
<td>.70</td>
</tr>
<tr>
<td>Age</td>
<td>0.96</td>
<td>.13</td>
</tr>
<tr>
<td>Control status</td>
<td>0.783</td>
<td>.20</td>
</tr>
<tr>
<td>Previous exacerbation</td>
<td>2.16</td>
<td>.009</td>
</tr>
<tr>
<td>Rhinitis (yes vs no)</td>
<td>0.76</td>
<td>.32</td>
</tr>
<tr>
<td>Smoking (yes vs no)</td>
<td>1.21</td>
<td>.55</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>1.02</td>
<td>.45</td>
</tr>
<tr>
<td>Basal percentage of predicted value of forced expiratory volume in 1 s</td>
<td>1.00</td>
<td>.17</td>
</tr>
<tr>
<td>Atopy (yes vs no)</td>
<td>1.36</td>
<td>.38</td>
</tr>
<tr>
<td>Korean version of the Mini-Mental State Examination</td>
<td>0.97</td>
<td>.35</td>
</tr>
<tr>
<td>Korean version of the Geriatric Depression Scale Short Form</td>
<td>1.47</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Adherence</td>
<td>0.62</td>
<td>.004</td>
</tr>
<tr>
<td>Inhaler technique</td>
<td>0.57</td>
<td>.001</td>
</tr>
</tbody>
</table>

Multi-disciplinary approach is necessary for elderly asthma patients.

Park HW, Cho SH et al. JAGS 2013
Diagnostic Challenges

- Lack of consensus guidelines
- Under-diagnosis of elderly asthma
- Difficulty in objective assessments
- ACOS (asthma-COPD overlap syndrome)
Underperception (patients)

- “This is just an aging process”.
- Reduced perception of bronchoconstriction
- Fear of admitting symptoms
- Underreporting: depression, cognitive functions, social isolation

No no, its okay, its not an asthma attack, you just took my breath away.
Underestimation (physicians)

- “Asthma should be rare in the elderly.”
- Frequent asthma-mimicking condition (dyspnea with wheeze)
  - COPD
  - Congestive heart failure
  - GERD
  - Chronic aspiration
  - Tumor
  - Obesity
Difficulty in objective assessments

- Poor spirometry performance (10-20% patients)
- Reduced bronchodilator responses
  - decreased β2 receptors in smooth muscles
  - airway remodeling d/t longstanding asthma
- Lack of reliable reference lung function data
- Prevalent history of smoking (especially, in males)
  → asthma? vs. COPD?
Increased hyperresponsiveness with aging

Trigg CJ et al. Thorax 1990
Deborah S et al. Chest 1999
Impaired bronchodilator response in elderly

Connolly et al. Chest 1995
Prevalence of obstructive airway diseases

(1) allergic disease consistent with asthma that is incompletely reversible or
(2) COPD with emphysema accompanied by reversible or partially reversible
airflow obstruction ➔ overlap syndrome

J Allergy 2011
Overlap syndrome increases with age

Gibson P et al. Thorax 2009
Lung function changes during 2-year follow-ups

Baseline FEV1/FVC

- 70.9% (≥0.70)
- 29.1% (<0.70%)

Best FEV1/FVC during last 1-yr

- 65.9%
- 11.7%
- 4.9%
- 17.5%

Asthma-COPD overlap group (22.4%)

Persistently ≥0.70
Worsened to <0.70
Recovered to ≥0.70
Persistently <0.70

Moon SD, Cho SH et al. WAC 2015 poster
Diagnostic details that affect management

- Age at onset
- Total and specific IgE levels
- Smoking or passive exposure
- Occupational exposures
- Domestic exposures to irritants, allergens, and stimulants of innate immunity
- Coexisting diseases
- Upper airway disease, sinusitis, and polyps
- Aspirin sensitivity
- β-Adrenergic blocking drugs, including eyedrops, and angiotensin-converting enzyme inhibitors
- Persistent airway obstruction despite therapy
- Abnormal chest radiographic or CT scan results
Overall asthma control

Current Control
- Symptoms
- Activity
- Lung function
- Reliever use

Future Risk
- Instability / Worsening
- Exacerbations
- Lung function loss
- Medication adverse reaction

Control of comorbid diseases
Control of environments / Education

Bateman ED J Allergy Clin Immunol. 2010
Exclusion of elderly asthma patients from RCTs

About 50% of elderly patients are excluded from RCT by the presence of comorbidities.

Battaglia et al. *Respiration* 2015
What should be the ‘treatment goal’?

- Aggressive pharmacotherapy may be harmful.
- Limited data on efficacy and ADR of asthma medication in elderly
- Fixed airway obstruction is frequent.
  - Individualized treatment goal should be set.
    (i.e., determination of personal best FEV1 with short course of steroids)
Parameters for Air trapping

Lee SM, Cho SH et al., in preparation

E/I ratio of LA < -910HU

FEV1 increase (% basal)
ICS in the elderly asthma

- Mainstay of asthma treatment in elderly population
- Potential concerns resulting from aging-related physical and functional changes and corticosteroid therapy
- Candidiasis
- Cataract and glaucoma
- Osteoporosis and fracture
- Pneumonia in patients with COPD and asthma
Role of ICS in the elderly asthma

Elderly asthma with ICS (—)
Elderly asthma without ICS (---)

Risk of rehospitalization or mortality %

Time from discharge months
Bone mineral density and cumulative ICS dose

Scatter plots for bone mineral density against logarithm of cumulative dose of inhaled corticosteroid. Regression lines derived from age-adjusted and sex-adjusted models, while keeping age and sex at their averages.

Wong et al. Lancet 2000
Non-vertebral fracture risk and ICS dose

Fig. 2. Forest plot of the risk of non-vertebral fracture per 1000 µg increase in dose of inhaled corticosteroids (ICS) (beclomethasone dipropionate or equivalent), area of box proportional to precision of estimate.
# Risk of pneumonia in asthma patients using ICS

### Table 4—Analysis Combining Type of ICS and Dose With Risk of Pneumonia or LRTI (n = 43,095)

<table>
<thead>
<tr>
<th>ICS Use in the Past 90 d</th>
<th>Cases, No. (%)</th>
<th>Control Subjects, No. (%)</th>
<th>OR</th>
<th>Adjusted OR&lt;sup&gt;a&lt;/sup&gt;</th>
<th>95% CI</th>
<th>Adjusted OR&lt;sup&gt;b&lt;/sup&gt;</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>No steroids</td>
<td>3,432 (50.1)</td>
<td>24,143 (66.5)</td>
<td>1.00</td>
<td>1.00</td>
<td>...</td>
<td>1.00</td>
<td>...</td>
</tr>
<tr>
<td>Beclomethasone low dose ≤ 200 µg</td>
<td>1,031 (15.0)</td>
<td>5,101 (14.1)</td>
<td>1.41</td>
<td>1.07</td>
<td>0.98-1.16</td>
<td>1.12</td>
<td>0.94-1.33</td>
</tr>
<tr>
<td>Beclomethasone high dose &gt; 200 µg</td>
<td>183 (2.7)</td>
<td>642 (1.8)</td>
<td>1.86</td>
<td>1.24</td>
<td>1.03-1.49</td>
<td>1.33</td>
<td>0.76-2.32</td>
</tr>
<tr>
<td>Budesonide low dose ≤ 200 µg</td>
<td>417 (6.1)</td>
<td>1,671 (4.6)</td>
<td>1.75</td>
<td>1.18</td>
<td>1.04-1.35</td>
<td>1.14</td>
<td>0.86-1.49</td>
</tr>
<tr>
<td>Budesonide high dose &gt; 200 µg</td>
<td>119 (1.7)</td>
<td>394 (1.1)</td>
<td>2.10</td>
<td>1.16</td>
<td>0.93-1.46</td>
<td>1.19</td>
<td>0.66-2.16</td>
</tr>
<tr>
<td>Fluticasone low dose ≤ 250 µg</td>
<td>774 (11.3)</td>
<td>2,491 (6.9)</td>
<td>2.17</td>
<td>1.39</td>
<td>1.25-1.55</td>
<td>1.33</td>
<td>1.04-1.68</td>
</tr>
<tr>
<td>Fluticasone high dose &gt; 250 µg</td>
<td>895 (13.1)</td>
<td>1,826 (5.0)</td>
<td>3.45</td>
<td>1.89</td>
<td>1.69-2.11</td>
<td>2.06</td>
<td>1.57-2.69</td>
</tr>
</tbody>
</table>

Individuals taking ciclesonide/mometasone were excluded from the analyses because of small numbers. See Table 2 and 3 legends for expansion of abbreviations.

<sup>a</sup>Adjusted for number of relievers in the past year, Charlson Comorbidity Index score, smoking, social class, and use of oral steroids in the past year.

<sup>b</sup>Restricted to individuals aged < 40 y who did not have bronchiectasis and did not change steroid in the previous 90 d and adjusted for number of relievers in the past year, Charlson Comorbidity Index score, smoking, social class, and use of oral steroids in the past year.
Inhaled \( \beta_2 \)-agonist: concerns in the elderly

- Frequent tremor (\( \beta_2 \)-stimulation in skeletal m.)
- Dysrhythmia (up to 65% and more risky in ischemic heart disease)
- Hypokalemia in patients on concomitant diuretics or insulin therapy, or with poor nutrition

*Baseline ECG, electrolyte levels should be checked.
LABA safety of COPD in the elderly

Death from Any Cause

- Placebo
- Salmeterol
- Fluticasone
- Combination therapy

HR, 0.825
(95% CI, 0.681–1.002)
P=0.052 (log-rank test)

No. of Patients

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Weeks 0</th>
<th>Weeks 24</th>
<th>Weeks 48</th>
<th>Weeks 72</th>
<th>Weeks 96</th>
<th>Weeks 120</th>
<th>Weeks 156</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>1524</td>
<td>1500</td>
<td>1464</td>
<td>1428</td>
<td>1399</td>
<td>1361</td>
<td>1293</td>
</tr>
<tr>
<td>Salmeterol</td>
<td>1521</td>
<td>1502</td>
<td>1481</td>
<td>1451</td>
<td>1417</td>
<td>1368</td>
<td>1316</td>
</tr>
<tr>
<td>Fluticasone</td>
<td>1534</td>
<td>1512</td>
<td>1487</td>
<td>1450</td>
<td>1409</td>
<td>1363</td>
<td>1288</td>
</tr>
<tr>
<td>Combination therapy</td>
<td>1533</td>
<td>1514</td>
<td>1487</td>
<td>1456</td>
<td>1426</td>
<td>1393</td>
<td>1339</td>
</tr>
</tbody>
</table>

Calverley et al. *NEJM* 2007
LTRA in elderly asthma

• Clinical evidence is lacking in the elderly.

• Previous retrospective or case-control studies suggested LTRA efficacy to be less in the elderly than in younger patients.

• However, better adherence profile of LTRA may be potentially helpful.
## Effectiveness of LTRA in the Elderly

### NHLBI Maximum Asthma Severity Subgroups

<table>
<thead>
<tr>
<th>Elderly patients</th>
<th>Mild n† (%)</th>
<th>Moderate n† (%)</th>
<th>Severe n† (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pulmonary function</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FEV₁ ≥ 10%; PEF ≥ 20 L/min</td>
<td>14 / 23 (61)</td>
<td>97 / 160 (61)</td>
<td>46 / 76 (61)</td>
</tr>
<tr>
<td>FEV₁ &lt; 10%; PEF &lt; 20 L/min</td>
<td>9 / 23 (39)</td>
<td>63 / 160 (39)</td>
<td>30 / 76 (39)</td>
</tr>
<tr>
<td><strong>Asthma symptoms</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 10%</td>
<td>13 / 24 (54)</td>
<td>104 / 165 (63)</td>
<td>52 / 74 (70)</td>
</tr>
<tr>
<td>&lt; 10%</td>
<td>11 / 24 (46)</td>
<td>61 / 165 (37)</td>
<td>22 / 74 (30)</td>
</tr>
</tbody>
</table>

NHLBI = National Heart, Lung, and Blood Institute; FEV₁ = forced expiratory volume in 1 second; and PEF = peak expiratory flow.

Effectiveness/safety of LTRA vs. LABA

- Claims database-based analysis in US elderly

<table>
<thead>
<tr>
<th>Event</th>
<th>ICS + LABA</th>
<th>ICS + LTRA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asthma hospitalization or ED visit</td>
<td>0.5 (0.46–0.53)</td>
<td>0.6 (0.54–0.68)</td>
</tr>
<tr>
<td>Asthma-related oral corticosteroid or antibiotic prescription</td>
<td>0.36 (0.34–0.39)</td>
<td>0.52 (0.46–0.58)</td>
</tr>
<tr>
<td>Cardiovascular hospitalization or ED visit</td>
<td>2.4 (2.3–2.5)</td>
<td>1.5 (1.3–1.6)</td>
</tr>
</tbody>
</table>
Adherence in a pragmatic study

<table>
<thead>
<tr>
<th>Table 3. Secondary Outcome Measures.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Outcome Measure</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td><strong>First-line controller therapy trial</strong></td>
</tr>
<tr>
<td><strong>Asthma exacerbations</strong></td>
</tr>
<tr>
<td>Any — no. of exacerbations</td>
</tr>
<tr>
<td>1 — no. of patients/total no. (%)</td>
</tr>
<tr>
<td>&gt;1 — no. of patients/total no. (%)</td>
</tr>
<tr>
<td><strong>Adherence</strong></td>
</tr>
<tr>
<td>No. of patients</td>
</tr>
<tr>
<td>Rate — %</td>
</tr>
<tr>
<td>Median</td>
</tr>
<tr>
<td>Interquartile range</td>
</tr>
<tr>
<td><strong>Add-on therapy trial</strong></td>
</tr>
<tr>
<td><strong>Asthma exacerbations</strong></td>
</tr>
<tr>
<td>Any — no. of exacerbations</td>
</tr>
<tr>
<td>1 — no. of patients/total no. (%)</td>
</tr>
<tr>
<td>&gt;1 — no. of patients/total no. (%)</td>
</tr>
<tr>
<td><strong>Adherence</strong></td>
</tr>
<tr>
<td>No. of patients</td>
</tr>
<tr>
<td>Rate — %</td>
</tr>
<tr>
<td>Median</td>
</tr>
<tr>
<td>Interquartile range</td>
</tr>
<tr>
<td>Adherence to inhaled glucocorticoid</td>
</tr>
<tr>
<td>No. of patients</td>
</tr>
<tr>
<td>Rate — %</td>
</tr>
<tr>
<td>Median</td>
</tr>
<tr>
<td>Interquartile range</td>
</tr>
</tbody>
</table>

Price et al. NEJM 2011
Theophylline in the elderly

- Rather complex issues in drug clearance
  1) Usually slower clearance (by 22-35%)
  2) Further decreased clearance by liver and hear diseases
  3) 80% faster clearance in smokers

- Side effects: insomnia, nausea, dizziness

- Risk of fatal toxicity: seizures, arrhythmia
  - narrow therapeutic ranges
  - close drug level monitoring (self overdose)
Anticholinergics

- Role in maintenance therapy is not established.
- However, it may be more useful in the elderly due to:
  - high frequency of COPD comorbidity
  - maintained muscarinic receptors in the elderly (unlike β2-adrenergic receptors)
- Side effects
  - dry mouth, constipation, glaucoma, BPH
Promising role of tiotropium

Tiotropium step-up therapy for uncontrolled asthma. NEJM 2010
Anticholinergics for asthma: genotype-based approach

Additive role of tiotropium in severe asthmatics and Arg16Gly in *ADRB2* as a potential marker to predict response

138 severe asthmatics

Conventional Tx + tiotropium

PFT q 4 weeks

Over 8 weeks

Responder
Non-Responder

FEV1 improve ≥15%

Assess 11 SNPs in CHRM1-3, Arg16Gly, Gln27Glu in ADRB2

*Park HW, Cho SH et al., Allergy 2009:64:778-7*
Additional effect of Tiotropium

- Distribution of % increase of FEV1 after tiotropium add

N = 30  Responders
\[ r = -0.312 \]
\( (P > 0.05) \)

N = 49  Non-responders

% increase in FEV1 before tiotropium add (from diagnosis to tiotropium add)

Park HW, Cho SH et al. *Allergy* 2009
Response of omalizumab in the elderly

Mean total asthma symptom score

The change from baseline

Omalizumab

Placebo

P = 0.0411

Maykut et al. J asthma 2008
Response of omalizumab in the elderly

Korn et al. Ann Allergy Asthma Immunol 2010
IgE-targeted therapy for non-atopic adult asthma

Garcia et al. Chest 2013
Frequent comorbidities

- Allergic rhinitis
- Rhinosinusitis
- COPD
- GERD
- Obesity
- Cardiovascular disease
- DM
- Dyslipidemia
- Depression

→ Polypharmacy
Non-pharmacologic interventions

- Controlling triggers
  - infection
  - irritant (smoke, dust, pollutant)
  - β-blocker
  - aspirin
  - ACE inhibitor

- Asthma education and adherence
Non-pharmacologic interventions

- **Asthma action plan**: how to self-manage asthma exacerbation
- **Family care**
- **Immediate availability of unscheduled contact**
Inhaler technique

- Poor inhaler technique is a major risk factor for asthma exacerbation in the elderly.

Park HW, Cho SH et al. In submission

Overcome Elderly Asthma

Multidimensional approach

Lancet 2010

- Behavioral factors
  - Education
  - Inhaler technique
  - Non-adherence

- Airway components
  - Airflow obstruction
  - Airway inflammation
  - Exercise intolerance
  - SOB
  - ADRs

- Risk factors
  - Smoking
  - GERD
  - CRS
  - Depression

- Comorbidities assess with both asthma and ageing
  - Obesity/GERD/Sleep disorder/Depression/
  - OSA/Cardiac dis/
  - COPD/Anemia/
  - Cataract/Osteoporosis
  - Polypharmacy
Elderly asthma: different and more complex

- Childhood-onset asthma
  - Atopy
  - Genetic

- Late-onset asthma
  - Smoking, obesity
  - Rhinosinusitis (enterotoxin IgE)

- Childhood
  - Young adulthood
  - Elderhood

Lifespan (age)

Multidimensional approaches

Overcome Asthma in the Elderly

- More comorbidity
- More heterogeneity
- Multi-factorial exacerbation
- More socioeconomic burden

- Longterm prognosis
- Pathogenesis (endotypes)
- Precision medicine

Summary
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- Ho-Joo Yoon, Sang-Heon Kim (Hanyang University)
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- Young-Gu Ji (Dankook University)
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- Yoon-Seok Chang, Sae-Hoon Kim (Bundang Seoul National University)
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- Byoung-Whui Choi (Chungang University)
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- An-Soo Jang (Soonchunhyang University)
- Dong-Ho Nam (Ajou University)
- Soon-Seog Kwon (Catholic University)
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