COPD & asthma & PFT

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12th Lecture Berlin Reviews in Internal Medicine Resident 2
Inflammatory airway diseases

Asthma
(Allergen sensitization)

Epithelial Cell

Mast cells

CD8 T lymphocytes
(Th2)

Bronchial construction
Airway hyper-responsiveness

Eosinophils

COPD cigarette smokers
Wood smoke (Biomass)

Alveolar Macrophages

CD8 T lymphocytes
(Tck)

Small airway fibrosis
Alveolar destruction

Neutrophils

Obstructive airway diseases
Definition of Asthma

- Airway inflammation
- Respiratory symptoms (vary overtime)
- Variable airflow limitation

- The diagnosis of asthma should be based on
  1) A history of characteristic symptom patterns
  2) An evidence of variable airflow limitation
     (from bronchodilator reversibility testing or other tests)
- Document evidence for the diagnosis before starting controller treatment
     (difficult to confirm diagnosis after treatment started)
- Asthma is characterized by airway inflammation and airway hyper-responsiveness
  (not necessary or sufficient to make the diagnosis)

Global Strategies for Asthma Management and Prevention GINA report 2015
Variable and reversible airflow limitation

- **Variability**: improvement or deterioration in symptoms and lung function over time
- **Reversibility**: rapid improvement in FEV$_1$ or PEFR after inhalation of rapid acting bronchodilator

![Diagram showing airflow variability and reversibility](image.png)

- FEV$_1$ or PEFR
- Normal lung function
- Exacerbation
- ICS
- No symptom

![Graphs showing FEV$_1$, Predict, Post-BD, Pre-BD over time](image.png)

- FEV$_1$
- Predict
- Post-BD
- Pre-BD

<table>
<thead>
<tr>
<th>Time (wk)</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td></td>
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<td></td>
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<tr>
<td>Exacerbation</td>
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<tr>
<td>ICS</td>
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<tr>
<td>No symptom</td>
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</tbody>
</table>
Lung function in asthma
Reversible or not fully reversible airflow obstruction

Expiratory Spirogram

- Normal
- Asthma (before BD)
- Asthma (after BD)

Flow volume loop

- Normal
- Asthma (before BD)
- Asthma (after BD)

Scoop pattern (concavity of expiratory limb)

Reversibility test using a short acting bronchodilator (Salbutamol 400 mcg)
# Pattern of respiratory symptoms

<table>
<thead>
<tr>
<th>Features are typical of asthma and if present increase the possibility that the patient has asthma</th>
<th>Features decrease the possibility that the patient has asthma</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>More than one symptom</strong> (wheeze, shortness of breath, cough and chest tightness) especially in adults</td>
<td><strong>Isolated cough</strong> with no other respiratory symptoms</td>
</tr>
<tr>
<td><strong>Symptoms worse</strong> at night or in the early morning</td>
<td><strong>Chronic production of sputum</strong></td>
</tr>
<tr>
<td><strong>Symptoms vary</strong> over time and in intensity</td>
<td><strong>Shortness of breath associated with dizziness, light-headedness, peripheral tingling</strong></td>
</tr>
<tr>
<td><strong>Symptoms are triggered by</strong> viral infection (cold), exercise, allergen exposure, change in weather, irritant such as care exhaust fume, smoke, strong smell</td>
<td><strong>Chest pain</strong></td>
</tr>
<tr>
<td></td>
<td>Exercise induced dyspnea <strong>Noisy inspiration</strong></td>
</tr>
</tbody>
</table>

Global Strategies for Asthma Management and Prevention GINA report 2015
Spirometry for determining airflow obstruction

low FEV$_1$/FVC ratio

<table>
<thead>
<tr>
<th></th>
<th>FEV$_1$</th>
<th>FVC</th>
<th>FEV$_1$/FVC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>4.150</td>
<td>5.200</td>
<td>0.8</td>
</tr>
<tr>
<td>Obstruction</td>
<td>2.350</td>
<td>3.900</td>
<td>0.6</td>
</tr>
</tbody>
</table>
Diagnostic criteria for reversible airflow obstruction

Global Strategies for Asthma Management and Prevention GINA report 2015

<table>
<thead>
<tr>
<th>Diagnostic features</th>
<th>Criteria for making diagnosis of asthma</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Confirmed expiratory airflow limitation</strong></td>
<td></td>
</tr>
<tr>
<td>Document airflow limitation AND</td>
<td>At least 1 during DX when FEV\textsubscript{1} is low and FEV\textsubscript{1}/FVC is reduced</td>
</tr>
</tbody>
</table>

| Document excessive variability in PFT (1 of below) | |
| Positive bronchodilator reversibility test | ↑ In FEV\textsubscript{1} > 12% and 200 ml from baseline 15 min after 200-400 mcg salbutamol |
| Excessive variability in twice daily PEF in 2 weeks | Average diurnal PEF variability >10% |
| Significant ↑ PFT after 4 week treatment | ↑ In FEV\textsubscript{1} > 12% and 200 ml (PFE >20%) after 4 wks RX |
| Positive exercise challenge test | ↓ In FEV\textsubscript{1} >10% and 200 ml from baseline |
| Positive bronchial challenge test | ↓ FEV\textsubscript{1} ≥ 20% (methacholine or histamine) or ↓ ≥ 15% (hyperventilation, hypertonic saline, mannitol) |
| Excessive variation in PFT between visits | Variation in FEV\textsubscript{1} > 12% and 200 ml (not PEF) between visits outside respiratory infection |
PEFR variability Measurement

Pre-bronchodilator value (X 3 times)
Using the same PEF meter device

PEFR (L/min)

<table>
<thead>
<tr>
<th>Time (days)</th>
<th>D1</th>
<th>D2</th>
<th>D3</th>
<th>D4</th>
<th>D5</th>
<th>D6</th>
<th>D7</th>
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</thead>
<tbody>
<tr>
<td>a.m.</td>
<td></td>
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<tr>
<td>p.m.</td>
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<td>a.m.</td>
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<td>a.m.</td>
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<tr>
<td>p.m.</td>
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</tbody>
</table>

PEF variability

= \frac{\text{PEF}_{\text{max}} - \text{PEF}_{\text{min}}}{\text{PEF}_{\text{max}} + \text{PEF}_{\text{min}}} \times 2

If >10% indicates variability

Min% max = \frac{\text{PEF}_{\text{min}}}{\text{PEF}_{\text{max}}}

Pre-bronchodilator PEFR morning every day in 1 week

if >80% no variability

Helen K Raddel et al. AJRCCM 2009

Within day PEF variability (diurnal pattern) over 1-2 week
Amplitude% mean = average \left(\text{day’s highest} - \text{lowest}\right)\text{ mean daily PEF}

Between day PEF variability
Min% Max = the lowest morning PEF (w/l 1 wk) / the highest PEF
Diagnostics test for patients suspected asthma

**Summary**

Selected diagnostic tools for suspected asthma

- **Patients with airflow obstruction**
  - Reversibility testing (FEV\(_1\) or PEFR)
  - Variability in PEFR

- **Patients without airflow obstruction**
  - Bronchial challenge testing (MCT)
  - Mannitol, saline challenge testing
  - Exercise testing
  - Test of airway inflammation

**Other investigations**
- CXR, CBC, SPT, RAST sIgE allergen and FVL loop
- Sputum Eo count
- Fe NO
Assessment asthma control in adult (3 components)

Assess asthma control
- Symptom control
- Future risk of adverse event

Assess treatment issue
- Document the patient current treatment step
  - Watch inhaler technique, adherence and side effect
  - Check patient written action plan
  - Ask about attitude and goal for medications

Assess co-morbidities
- Rhinitis
- Rhinosinusitis
- Gastroesophageal reflux
- Obesity
- Obstructive sleep apnea
- Depression
- Anxiety

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Assess symptom control (in the past 4 wks)
- Identify risk factor of exacerbation
- Fixed airflow limitation
- Side effect
- Measure PFT
Asthma symptom control
(Exclude FEV$_1$ from control assessment)

In the past 4 weeks, has the patient had:

- Daytime asthma symptoms (>2/wk) Yes □ No □
- Any night awakening due to asthma Yes □ No □
- Reliever use for symptoms (>2/wk) Yes □ No □
- Any activity limitation due to asthma Yes □ No □

None of these 1-2 of these 3-4 of these

* WC= well controlled, PC= Partly controlled and UC = Uncontrolled asthma

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Risk factor of poor asthma outcome

Poor asthma outcome

Risk factors of exacerbation
- Uncontrolled symptoms
- Excessive SABA use >200/mo
- Inadequate ICS
- Low FEV₁ (<60% predicted)
- Exposure: smoking, allergen
- Major psychological problems
- Co-morbidities (AR, obesity)
- Sputum of blood eosinophilia
- Pregnancy
- ICU or intubation for asthma
- ≥1 severe exacerbation in last 12 mo

Risk factors for developing fixed AO
- Lack of ICS treatment
- Exposure: tobacco, noxious, chemical and occupation (ACOS)
- Chronic mucus secretion

Risk factors of medication side effect
- Systemic: frequent OCS, high and potent ICS and taking P450 inhibitor
- Local: high dose and potent inhibitor, poor inhale technique

Modifiable factors of exacerbation

Independent risk factors of exacerbation

Having 1 or more risk factors increase risk of exacerbation
even if symptoms are well controlled

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Asthma composite scores
(ACT, ACQ and ATAQ)

<table>
<thead>
<tr>
<th>Question topics</th>
<th>ACT (4 weeks)</th>
<th>ATAQ (4 weeks)</th>
<th>ACQ (1 week)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Limits daily activities</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>Shortness of breath</td>
<td>✔</td>
<td></td>
<td>✔</td>
</tr>
<tr>
<td>Disrupts sleep</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>SABA use</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>Effect of global control</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>Frequency of wheeze</td>
<td></td>
<td></td>
<td>✔</td>
</tr>
<tr>
<td>Pre-bronchodilator FEV₁</td>
<td></td>
<td></td>
<td>✔</td>
</tr>
</tbody>
</table>

Asthma Control Test (ACT) and childhood Asthma Control Test
Asthma Therapy Assessment Questionnaire (ATAQ)
Asthma Control Questionnaire (ACQ)-7 (With FEV₁)
Short form ACQ-5 or ACQ-6 (Without FEV₁)

ACT (Nathan et al., 2004)
ATAQ (Vollmer et al., 1999)
ACQ (Juniper et al., 1999)
<table>
<thead>
<tr>
<th>คำถาม 1</th>
<th>ในช่วง 4 สัปดาห์ที่ผ่านมา บ่อยแค่ไหนที่โรคหืดทำให้คุณไม่สามารถทำงานที่เคยทำได้ไม่ว่าจะเป็นงานที่ทำงานที่โรงเรียน หรือที่บ้าน</th>
</tr>
</thead>
<tbody>
<tr>
<td>ติดลวดลาย</td>
<td>ป่วยมาก</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>คำถาม 2</th>
<th>ในช่วง 4 สัปดาห์ที่ผ่านมา บ่อยแค่ไหนที่คุณรู้สึกหายใจไม่ดี</th>
</tr>
</thead>
<tbody>
<tr>
<td>มากกว่า 1 ครั้งต่อวัน</td>
<td>วันละครั้ง</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>คำถาม 3</th>
<th>ในช่วง 4 สัปดาห์ที่ผ่านมา บ่อยแค่ไหนที่คุณมีอาการของโรคหืด (หายใจมีเสียงวี๊ดๆ ไอหายใจไม่ออก หน้าอกหรือเจ็บหน้าอก) จนทำให้ต้องตื่นขึ้นกลับดึก หรือตื่นเช้ากว่าปกติ</th>
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</thead>
<tbody>
<tr>
<td>4 ครั้งหรือมากกว่าต่อวัน</td>
<td>2-3 ครั้งต่อสัปดาห์</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>คำถาม 4</th>
<th>ในช่วง 4 สัปดาห์ที่ผ่านมา คุณต้องใช้ยาสูดพ่นขยายหลอดลมชนิดออกฤทธิ์เร็ว หรือยาเม็ดขยายหลอดลมชนิดออกฤทธิ์เร็วบ่อยแค่ไหนเพื่อช่วยให้คุณหายใจได้ดีขึ้น</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 ครั้งหรือมากกว่าต่อวัน</td>
<td>1-2 ครั้งต่อวัน</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>คำถาม 5</th>
<th>ในช่วง 4 สัปดาห์ที่ผ่านมา คุณคิดว่าคุณสามารถควบคุมโรคหืดของคุณได้ดีมากน้อยแค่ไหน</th>
</tr>
</thead>
<tbody>
<tr>
<td>ควบคุมไม่ได้เลย</td>
<td>ควบคุมได้ไม่ค่อยดี</td>
</tr>
</tbody>
</table>

นำคะแนนในแต่ละข้อมาบวกกันเป็นคะแนนรวม
ACT as a predictor of GINA-defined asthma control level

n=2949

Thomas et al. Prim Care Resp J 2009
ACT score and risk of subsequent exacerbation over 12 months

<table>
<thead>
<tr>
<th>ACT score</th>
<th>Odds Ratio (Relative to ACT score of 20)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>19</td>
<td>1.09</td>
<td>1.07-1.11</td>
</tr>
<tr>
<td>18</td>
<td>1.21</td>
<td>1.19-1.23</td>
</tr>
<tr>
<td>17</td>
<td>1.33</td>
<td>1.31-1.35</td>
</tr>
<tr>
<td>16</td>
<td>1.46</td>
<td>1.44-1.48</td>
</tr>
<tr>
<td>15</td>
<td>1.60</td>
<td>1.58-1.62</td>
</tr>
</tbody>
</table>

ACT of 15 means 60% greater risk of exacerbation than if ACT is 20

Long term goals
Asthma management

Long term goal

- Good control of symptoms
- Maintain normal activity level
- To minimize future risk of exacerbations
- To minimize fixed airflow obstruction
- To minimize side effects

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## Categories of asthma medications

**GINA 2015**

### Controller medications
- Regular maintenance level
- Reduce airway inflammation
- Reduced future risk (Exacerbation & decline in lung function)

### Reliever (Rescue) medications
- As need relieve of breakthrough symptoms (worsening of asthma or exacerbation)
- Short term prevention of EIB

### Added on therapies for severe asthma
- Consider when persistent symptoms/exacerbation despite optimized treatment (High ICS/LABA)
- Treatment of modifiable risk factors

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<table>
<thead>
<tr>
<th>Preferred controller choice</th>
<th>Other controller choice</th>
<th>Reliever</th>
<th>STEP 1</th>
<th>STEP 2</th>
<th>STEP 3</th>
<th>STEP 4</th>
<th>STEP 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consider low dose ICS</td>
<td>Leukotriene receptor antagonist Intermittent ICS</td>
<td>As needed short-acting β2 agonist (SABA)</td>
<td>Consider low dose ICS</td>
<td>Low dose ICS</td>
<td>Mod/high dose ICS Low dose ICS +LTRA (or + Theophylline)</td>
<td>Add tiotropium High dose ICS +LTRA (or + Theophylline)</td>
<td>Refer to add-on treatment e.g. (Anti-IgE)</td>
</tr>
</tbody>
</table>

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**Global Strategies for Asthma Management and Prevention GINA report 2015**

**REVIEWS RESPONSE**

**ASSESS**

**ADJUST TREATMENT**
## Recommended option initial controller treatments

<table>
<thead>
<tr>
<th>Presenting symptoms</th>
<th>Preferred initial controller</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asthma symptoms or need for SABA <strong>less than twice a month</strong>;</td>
<td>No controller <em>(Evidence D)</em></td>
</tr>
<tr>
<td>No waking up due to asthma in the last month, and</td>
<td></td>
</tr>
<tr>
<td>No risk factor for exacerbation, &amp; exacerbation in last year</td>
<td></td>
</tr>
<tr>
<td><strong>Infrequent asthma symptoms, but patient has 1 or more risk factor for exacerbation</strong></td>
<td>Low dose ICS <em>(Evidence D)</em></td>
</tr>
<tr>
<td>Asthma symptoms or need for SABA <strong>between 2/month and 2/week</strong>, or patients <strong>wake due to asthma 1 or more/month</strong></td>
<td>Low dose ICS <em>(Evidence B)</em></td>
</tr>
<tr>
<td>Asthma symptoms or need for SABA <strong>more than 2/week</strong></td>
<td>Low dose ICS <em>(Evidence A)</em></td>
</tr>
<tr>
<td>Other (less effective)options are LTRA or theophylline</td>
<td></td>
</tr>
<tr>
<td>Troublesome asthma symptoms most day: or waking due to <strong>asthma 1/week or more</strong>, especially <strong>if any risk factor exist</strong></td>
<td>Medium ICS <em>(Evidence A)</em> or Low dose ICS/LABA <em>(Evidence A)</em></td>
</tr>
<tr>
<td>Initial presentation is with severely uncontrolled asthma or with an <strong>acute exacerbation</strong></td>
<td>Short course oral CS and start regular controllers are High dose ICS <em>(Evidence A)</em> or Moderate ICS/LABA <em>(Evidence D)</em></td>
</tr>
</tbody>
</table>

Global Strategies for Asthma Management and Prevention GINA report 2015
Global Strategies for Asthma Management and Prevention GINA report 2015

Other options:
Low dose ICS should be considered for patients at risk of exacerbation

**STEP 1**
Consider low dose ICS

**STEP 2**
Low dose ICS
- Leukotriene receptor antagonist
- Intermittent ICS

**STEP 3**
Low dose ICS-LABA
- Mod/high dose ICS
- Low dose ICS +LTRA (or + Theophylline)

**STEP 4**
Med/high ICS/LABA
- Add tiotropium
- High dose ICS +LTRA (or + Theophylline)

**STEP 5**
Refer to add-on treatment e.g. (Anti-IgE)
- Add tiotropium
- Add low dose OCS

Preferred option:
- As needed short-acting β2 agonist (SABA)
- As needed SABA or low dose ICS/fomoterol

Ipatropium, oral SABA or short acting theophylline are alternative to SABA as reliever
**Global Strategies for Asthma Management and Prevention GINA report 2015**

**Preferred option:**
Regular low dose ICS plus as-needed reliever medication

**STEP 1**
Consider low dose ICS

**STEP 2**
Low dose ICS
- Leukotriene receptor antagonist
- Intermittent ICS
- As needed short-acting β2 agonist (SABA)

**STEP 3**
Low dose ICS-LABA
- Mod/high dose ICS
- Low dose ICS + LTRA (or + Theophylline)

**STEP 4**
Med/ high ICS /LABA
- Add tiotropium
- High dose ICS + LTRA (or + Theophylline)

**STEP 5**
Refer to add-on treatment e.g. (Anti-IgE)
- Add tiotropium
- Add low dose OCS
- Add as needed SABA or low dose ICS/fomoterol

**Other options:** LTRA (less effective than ICS)
Unable or unwilling to use ICS, experience intolerable S/E, or concomitant allergic rhinitis

Low dose ICS-LABA as initial controller
**Options not recommended:** sustained release theophylline and chromones
## Equivalent dose of inhaled corticosteroid

### Adult and adolescents (12 y and older)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Low</th>
<th>Medium</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beclonethasone dipropionate (CFC)</td>
<td>200-500</td>
<td>&gt;500-1000</td>
<td>&gt;1000</td>
</tr>
<tr>
<td>Beclonethasone dipropionate (HFA)</td>
<td>100-200</td>
<td>&gt;200-400</td>
<td>&gt;400</td>
</tr>
<tr>
<td>Budesonide (DPI)</td>
<td>200-400</td>
<td>&gt;400-800</td>
<td>&gt;800</td>
</tr>
<tr>
<td>Ciclesonide (HFA)</td>
<td>80-160</td>
<td>160-320</td>
<td>&gt;320</td>
</tr>
<tr>
<td>Fluticasone propionate (DPI)</td>
<td>100-250</td>
<td>250-500</td>
<td>&gt;500</td>
</tr>
<tr>
<td>Fluticasone propionate (HFA)</td>
<td>100-250</td>
<td>250-500</td>
<td>&gt;500</td>
</tr>
<tr>
<td>Mometasone furoate</td>
<td>110-220</td>
<td>220-440</td>
<td>&gt;440</td>
</tr>
<tr>
<td>Triamcinolone</td>
<td>400-1000</td>
<td>&gt;1000-2000</td>
<td>&gt;2000</td>
</tr>
</tbody>
</table>
ICS-LABA as initial maintenance

- For adult and adolescent not previously using controller treatment
- Combined low dose ICS-LABA reduces symptoms and improves PFT compared with low dose ICS alone.
- It is more expensive and no further reduce risk of exacerbation compared with ICS alone

Global Strategies for Asthma Management and Prevention GINA report 2015
**Preferred option**
Combination low dose ICS/LABA as maintenance plus as needed SABA
or
Combination low dose ICS/formoterol (budesonide or beclomethasone) as both maintenance and reliever

**Other options**
Increase ICS to medium dose, (less effective than adding a LABA (Evidence A)
Low dose ICS plus either LTRA (Evidence A)
low dose ICS plus sustained release theophylline (Evidence B)
Persistent asthmatic using of ICS 400-800 µg/day of BDP equivalent

- Assess inhaler techniques and improve delivery technique
- Check compliance
- Exclude avoidable trigger factors
- Exclude concomitant diseases

Persistent asthmatic with preserved airway caliber
or with allergic rhinitis

Add LTRA

Symptomatic control

- No
  - Add LABA

Persistent asthmatic with impaired airway caliber

Add LABA

Symptomatic control

- Yes
  - Arrange further review
- No
  - Add LTRA

Graeme P Currie et al Chest 2005
Please check!
Before considering step up

- Confirm the symptoms are due to asthma
- Incorrect inhalation technique
- Poor adherence
- Environmental exposure

Global Strategies for Asthma Management and Prevention GINA report 2015
Flow volume loop in the diseases

- Normal
- Mild obstructive defect
- Severe obstructive defect

Variable intrathoracic Upper airway obstruction

Variable Extra-thoracic Upper airway obstruction

Fixed Extra or intrathoracic Upper airway obstruction

Restriction (pulmonary fibrosis)

Restriction (kyphoscoliosis)

Pre and post bronchodilator
Inhaled therapy devices for asthma and COPD

**Metered dose inhaler (MDIs)**
- Conventional pressurized MDI
- Soft mist inhaler (SMI)
- Device adjunct (spacer)

**Dry-powder inhaler (DPI)**
1) Single dose DPI (capsule)
   - Handihaler
   - Breezhaler
2) Multiple dose DPI
   - Turbuhaler
   - Accuhaler
   - Easyhaler

**Nebulizers**
- Small volume nebulizer (SVN)
  - Ultrasonic
Inhaled drug deposition from various inhalers

Rau JL Jr. Respiratory Care Pharmacology. 2002
<table>
<thead>
<tr>
<th>Physical and mental impairment</th>
<th>Pressurized MDI</th>
<th>Pressurized MDI with chamber</th>
<th>Dry Powder Inhaler (DPI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased peak inspiratory flow rate</td>
<td>✔</td>
<td>✔</td>
<td>✗</td>
</tr>
<tr>
<td>Impaired cognition</td>
<td>?</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>Impaired manual dexterity</td>
<td>✗</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>Impaired press and breath coordination</td>
<td>✗</td>
<td>✔</td>
<td>✔</td>
</tr>
</tbody>
</table>

P Gibson. Asthma in Elderly Lancet Respiratory 2009
### 4C for correct inhaler technique in asthma

<table>
<thead>
<tr>
<th>Choose</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Choose an appropriate device before prescribing. Consider medication options, arthritis, patient skills and cost. For ICS by pMDI, prescribe a spacer</td>
</tr>
<tr>
<td>• Avoid multiple different inhaler types if possible</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Check</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Check technique at every opportunity – “Can you show me how you use your inhaler at present?”</td>
</tr>
<tr>
<td>• Identify errors with a device-specific checklist</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Correct</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Give a physical demonstration to show how to use the inhaler correctly</td>
</tr>
<tr>
<td>• Check again (up to 2-3 times)</td>
</tr>
<tr>
<td>• Re-check inhaler technique frequently, as errors often recur within 4-6 weeks</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Confirm</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Can you demonstrate correct technique for the inhalers you prescribe?</td>
</tr>
<tr>
<td>• Brief inhaler technique training improves asthma control</td>
</tr>
</tbody>
</table>

Global Strategies for Asthma Management and Prevention GINA report 2015
Role of healthcare worker in improving patient inhaler skill and technique
Global Airway Disease Beyond Allergy

Therapeutic options
Efficacy in nasal and ocular symptoms

<table>
<thead>
<tr>
<th>Drug</th>
<th>Sneezing</th>
<th>Rhinorrhea</th>
<th>Nasal obstruction</th>
<th>Nasal itch</th>
<th>Ocular symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>INS</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Oral AH</td>
<td>++</td>
<td>++</td>
<td>+</td>
<td>+++</td>
<td>++</td>
</tr>
<tr>
<td>Topical decongestant</td>
<td>0</td>
<td>0</td>
<td>++++</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Chromone</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Anticholinergic</td>
<td>0</td>
<td>++</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>LTRAs</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
</tbody>
</table>

*Alleviates ocular symptoms only when administered as eye drops*

Currently approved combination ICS-LABA

<table>
<thead>
<tr>
<th>ICS</th>
<th>LABA</th>
<th>Brand Names</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluticasone propionate</td>
<td>Salmeterol xinofoate</td>
<td>SERETIDE® or ADVAIR</td>
</tr>
<tr>
<td>Budesonide</td>
<td>Formoterol fumarate</td>
<td>SYMPLICITY®</td>
</tr>
<tr>
<td>Beclomethasone</td>
<td>Formoterol fumarate</td>
<td>FOSTER®</td>
</tr>
<tr>
<td>Mometasone furoate</td>
<td>Formoterol fumarate</td>
<td>ZENHALE® or DURELA®</td>
</tr>
<tr>
<td>Fluticasone propionate</td>
<td>Formoterol fumarate</td>
<td>FLUTIFORM®</td>
</tr>
<tr>
<td>Fluticasone furoate</td>
<td>Vilanterol</td>
<td>RELVAR ® or BREO ®</td>
</tr>
</tbody>
</table>

Adding LABA to the same dose of ICS provides additional improvement in symptoms and PFT with a reduced exacerbation

GINA 2015
## β agonists pharmacology

<table>
<thead>
<tr>
<th>Properties</th>
<th>Salbutamol</th>
<th>Formoterol</th>
<th>Salmeterol</th>
<th>Indacaterol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Selectivity for b₂-adrenoceptors</td>
<td>Moderate</td>
<td>High</td>
<td>High</td>
<td>High</td>
</tr>
<tr>
<td>Affinity for b₂-adrenoceptors (pKi)</td>
<td>Low</td>
<td>High</td>
<td>High</td>
<td>High</td>
</tr>
<tr>
<td></td>
<td>(6.12 ± 0.09)</td>
<td>(7.84 ± 0.05)</td>
<td>(9.19 ± 0.12)</td>
<td>(7.36 ± 0.06)</td>
</tr>
<tr>
<td>Onset of bronchodilator action (min)</td>
<td>Quick</td>
<td>Quick</td>
<td>Slow</td>
<td>Quick</td>
</tr>
<tr>
<td></td>
<td>(11.0 ± 4.0)</td>
<td>(5.8 ± 0.7)</td>
<td>(19.4 ± 4.3)</td>
<td>(7.8 ± 0.7)</td>
</tr>
<tr>
<td>Duration of bronchodilator action (hours)</td>
<td>Short</td>
<td>Long</td>
<td>Long</td>
<td>Longer</td>
</tr>
<tr>
<td></td>
<td>(3–6)</td>
<td>(12 )</td>
<td>(12)</td>
<td>(24)</td>
</tr>
<tr>
<td>Efficacy (agonist)</td>
<td>Partial</td>
<td>Complete</td>
<td>Partial</td>
<td>Complete</td>
</tr>
<tr>
<td>Potency (EC₅₀)</td>
<td>High</td>
<td>High</td>
<td>High</td>
<td>High</td>
</tr>
<tr>
<td></td>
<td>(8.43 ± 0.22)</td>
<td>(9.84 ± 0.22)</td>
<td>(8.36 ± 0.16)</td>
<td>(8.82 ± 0.41)</td>
</tr>
<tr>
<td>Intrinsic efficacy (E_max % of isoprenaline)</td>
<td>High</td>
<td>High</td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td></td>
<td>(47 ± 1)</td>
<td>(90 ± 1)</td>
<td>(38 ± 1)</td>
<td>(73 ± 1)</td>
</tr>
</tbody>
</table>
The maintenance and reliever therapy

• In at risk patients, the ICS/formoterol maintenance and reliever regimen significantly reduces exacerbation and provides similar level of asthma control at relatively low dose ICS, compared with a fixed dose of ICS/LABA as maintenance treatment or a higher dose ICS, both with as needed SABA

• Low dose Budesonide            Formoterol fumarate
• Low dose Beclomethasone        Formoterol fumarate

Global Strategies for Asthma Management and Prevention GINA report 2015
Two approaches for combination therapies

**Conventional approach**
- Optimised daily maintenance dose
  - ICS+LABA fixed combination
- Symptom relief
  - SABA

**Single Maintenance and Reliever Therapy**
- Optimised daily maintenance dose
- Symptom relief and a timely increase in anti-inflammatory therapy
  - ICS+formoterol SMART
Global Strategies for Asthma Management and Prevention GINA report 2015

**Preferred option**
Combination low dose ICS/formoterol as maintenance and reliever treatment or Combination medium dose ICS/LABA plus as needed SABA

**STEP 1**
Low dose ICS

**STEP 2**
Low dose ICS-LABA
- Consider low dose ICS
- Leukotriene receptor antagonist
- Intermittent ICS

**STEP 3**
Med/ high ICS /LABA
- Mod/high dose ICS
- Low dose ICS +LTRA (or + Theophylline)

**STEP 4**
Add tiotropium
- High dose ICS +LTRA (or + Theophylline)
- Add low dose OCS

**STEP 5**
Refer to add-on treatment e.g. (Anti-IgE)

**Preferred controller choice**
- Combination low dose ICS/formoterol as maintenance and reliever treatment or
- Combination medium dose ICS/LABA plus as needed SABA

**Other controller choice**
- Low dose ICS
- As needed short-acting β2 agonist (SABA)

**Reliever**
- As needed SABA or low dose ICS/formoterol

**Tiotropium soft mist inhaler** added on therapy for patient with history of exacerbation

**High dose ICS/LABA**

**High dose ICS** (3-6 month trial basis)

**Low dose ICS plus LABA plus third controller (LTRA or SR theophylline)**
Muscarinic and β2 Adrenergic receptor distribution in human airways

Comparison of effect for anti-cholinergic and β adrenergic bronchodilators

<table>
<thead>
<tr>
<th></th>
<th>Anticholinergic</th>
<th>B agonist</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset</td>
<td>Slightly slower</td>
<td>Faster</td>
</tr>
<tr>
<td>Peak onset</td>
<td>Slower</td>
<td>Faster</td>
</tr>
<tr>
<td>Duration</td>
<td>Longer</td>
<td>Slower</td>
</tr>
<tr>
<td>Tremor</td>
<td>None</td>
<td>Yes</td>
</tr>
<tr>
<td>Fall of PaO₂</td>
<td>None</td>
<td>Yes</td>
</tr>
<tr>
<td>Tolerance</td>
<td>None</td>
<td>Yes</td>
</tr>
<tr>
<td>Site of action</td>
<td>Large, central airway</td>
<td>Central and peripheral airways</td>
</tr>
</tbody>
</table>

Adapted from J Haughney Respiratory Medicine. 2010; 3 125-131
Preferred option: referral to specialist investigation and consideration of add-on treatment

- Anti-IgE treatment (omalizumab) (Evidence A)
- Sputum guided treatment (Evidence A)
- Add-on tiotropium by soft-mist inhaler (Evidence B)
- Bronchial thermoplasty (Evidence B)
- Add-on low dose oral corticosteroid (Evidence D)
### Global Strategies for Asthma Management and Prevention GINA report 2015

#### Preferred controller choice

<table>
<thead>
<tr>
<th><strong>STEP 1</strong></th>
<th><strong>STEP 2</strong></th>
<th><strong>STEP 3</strong></th>
<th><strong>STEP 4</strong></th>
<th><strong>STEP 5</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Consider low dose ICS</td>
<td>Low dose ICS</td>
<td>Low dose ICS-LABA</td>
<td>Med/ high ICS /LABA</td>
<td>Refer to add-on treatment e.g. (Anti-IgE)</td>
</tr>
</tbody>
</table>

#### Other controller choice

<table>
<thead>
<tr>
<th><strong>Consider low dose ICS</strong></th>
<th><strong>Leukotriene receptor antagonist</strong></th>
<th><strong>Mod/high dose ICS</strong></th>
<th><strong>Add tiotropium</strong></th>
<th><strong>Add tiotropium</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Intermittent ICS</td>
<td></td>
<td>Low dose ICS</td>
<td>High dose ICS</td>
<td>Add low dose OCS</td>
</tr>
<tr>
<td></td>
<td></td>
<td>+LTRA (or + Theophylline)</td>
<td>+LTRA (or + Theophylline)</td>
<td></td>
</tr>
</tbody>
</table>

#### Reliever

<table>
<thead>
<tr>
<th><strong>As needed short acting β2 agonist SABA</strong></th>
<th><strong>As needed SABA or low dose ICS/formoterol</strong></th>
</tr>
</thead>
</table>

**STEP 5**
Referring to add-on treatment, e.g., Anti-IgE.
Medication changes for W-AAP

- **Increase frequency of SABA** or low dose ICS/FORM

- **Increase ICS component** 2 x dose to high dose (2000 mg BDP equivalent)

- **ICS/FORM**: BUD/FORM or BDP/FORM
  - Maintenance ICS/FOR
  - 4 x Maintenance ICS/FORM (<72 µg FORM/d)
  - **Maintenance & reliever ICS/FORM**
  - Continue maintenance & ↑ Reliever ICS/FORM (<72 µg/d)

- **ICS/SALM**
  - Maintenance ICS/SAML → ↑ dose to highest
  - Consider adding separate ICS inhaler for higher ICS

- **Oral prednisolone** 1 mg/kg up to 50 mg/d 5-7 d

Global Strategies for Asthma Management and Prevention GINA report 2015
Time course of asthma control
(After ICS treatment)

- No night symptoms
- FEV1
- Sputum eosinophils
- No SABA use
- AHR

<table>
<thead>
<tr>
<th>Current step</th>
<th>Current medication and dose</th>
<th>Options for stepping down</th>
<th>Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Step 5</strong></td>
<td><strong>High dose ICS/LABA plus OCS</strong></td>
<td><strong>Continue high dose ICS/LABA and reduce OCS</strong>&lt;br&gt;Use sputum guided for reducing OCS&lt;br&gt;Alternate day OCS treatment&lt;br&gt;Refer to expert advice</td>
<td>D B D D</td>
</tr>
<tr>
<td><strong>Step 4</strong></td>
<td><strong>Mod to high ICS/LABA</strong>&lt;br&gt;Med ICS/formoterol as maintenance reliever&lt;br&gt;High dose ICS plus second controller</td>
<td><strong>Continue ICS/LABA with 50% reduction ICS component (available formulation)</strong>&lt;br&gt;Discontinue LABA is likely lead to deteriorate&lt;br&gt;Reduce maintenance ICS/formoterol to low dose and continue as needed ICS/formoterol&lt;br&gt;Reduce ICS to 50% and continue second controller</td>
<td>B A D B</td>
</tr>
<tr>
<td><strong>Step 3</strong></td>
<td><strong>Low ICS/LABA maintenance</strong></td>
<td><strong>Reduce ICS/LABA to once daily</strong>&lt;br&gt;Discontinue LABA is likely lead to deteriorate</td>
<td>D A</td>
</tr>
<tr>
<td><strong>Step 2</strong></td>
<td><strong>Low dose ICS</strong></td>
<td><strong>Once daily dosing (budesonide, ciclesanide, mometasone)</strong>&lt;br&gt;Consider stop controller if there is no symptoms for 6-12 and no risk factors&lt;br&gt;Cessation of ICS in adult is not advised</td>
<td>A D A</td>
</tr>
</tbody>
</table>
## Pregnancy drug safety
**(US FDA drug safety in pregnancy)**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Pregnancy safety</th>
<th>Lactation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ICS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beclomethasone</td>
<td>C</td>
<td>Unknown</td>
</tr>
<tr>
<td>Budesonide</td>
<td>B</td>
<td>Unknown</td>
</tr>
<tr>
<td>Ciclesonide</td>
<td>C</td>
<td>Unknown</td>
</tr>
<tr>
<td>Fluticasone</td>
<td>C</td>
<td>Unknown</td>
</tr>
<tr>
<td>Mometasone</td>
<td>C</td>
<td>Unknown</td>
</tr>
<tr>
<td><strong>LABA</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Formoterol</td>
<td>C</td>
<td>Unknown</td>
</tr>
<tr>
<td>Salmeterol</td>
<td>C</td>
<td>Unknown</td>
</tr>
<tr>
<td><strong>Systemic corticosteroids</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>C</td>
<td>Probably safe</td>
</tr>
<tr>
<td>Hydrocortisone</td>
<td>C</td>
<td>Probably safe</td>
</tr>
<tr>
<td>Methylprednisolone</td>
<td>C</td>
<td>Probably safe</td>
</tr>
<tr>
<td>Prednisone</td>
<td>C</td>
<td>Probably safe</td>
</tr>
<tr>
<td><strong>SABA</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Albuterol</td>
<td>C</td>
<td>Probably safe</td>
</tr>
<tr>
<td>Levalbuterol</td>
<td>C</td>
<td>Unknown</td>
</tr>
<tr>
<td>Terbutaline</td>
<td>C</td>
<td>Probably safe</td>
</tr>
<tr>
<td>Theophylline</td>
<td>C</td>
<td>Probably safe</td>
</tr>
<tr>
<td><strong>SAMA</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ipratropium bromide</td>
<td>B</td>
<td>Unknown</td>
</tr>
<tr>
<td><strong>Leukotriene inhibitors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Montelukast</td>
<td>B</td>
<td>Unknown</td>
</tr>
<tr>
<td>Zafirlukast</td>
<td>B</td>
<td>Possibly unsafe</td>
</tr>
<tr>
<td>Zileuton</td>
<td>C</td>
<td>Probably safe</td>
</tr>
<tr>
<td>Prednisone</td>
<td>C</td>
<td>Probably safe</td>
</tr>
<tr>
<td><strong>Mast-cell stabilizers</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nedocromil</td>
<td>B</td>
<td>Unknown</td>
</tr>
<tr>
<td>Cromolyn</td>
<td>B</td>
<td>Unknown</td>
</tr>
<tr>
<td>Omalizumab</td>
<td>B</td>
<td>Unknown</td>
</tr>
</tbody>
</table>
Difficult of controlling asthma
With available treatment
Summary approach

Severe asthma
(requiring high intensity of treatments)

Good control if on high intensity treatment

Poor control despite high intensity treatment

Potentially treatment responsive but with persistent problems
(Poor compliance, inhaler technique, allergen exposure and smoking)

Persistent co-morbidities
• Psychosocial aspect
• Reflux disease
• Allergic rhinitis

Treatment resistance (Refractory) asthma
Biologic agents
Targeted therapies

Difficult to control asthma

Asthma Treatment Goals and Key Strategies
To control symptoms and minimize future risk

Global Strategies for Asthma Management and Prevention GINA report 2015

1. Medications
   - Treating modifiable risk factors
   - Non pharmacological therapies and strategies

2. Guided asthma action plan (Written asthma action plan)
   - Self monitoring
   - Skill training (Inhaler skills) and adherence

3. Asthma with co-morbidities
   - Asthma with special conditions
The 10 leading causes of death in the World

2012

- Ischemic heart disease: 7.4 million
- Stroke: 6.7 million
- COPD: 3.1 million
- LRTI: 3.7 million
- Trachea, bronchus & lung neoplasm: 1.6 million
- HIV/AIDS: 1.5 million
- Diarrhea: 1.5 million
- DM: 1.5 million
- Road accident: 1.3 million
- Hypertension: 1.1 million

COPD is a leading cause of morbidity and mortality worldwide.

http://www.who.int/mediacentre/factsheets/fs310/en/
Definition COPD (GOLD 2015)

- COPD is a common preventable and treatable disease, is characterized by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lung to noxious particles or gases.
- Exacerbations and co-morbidities contribute to the overall severity in individual patients.

GOLD Guideline 2015
Characteristic COPD pathology

- Small airway diseases
  - Obstructive bronchiolitis

- Mucus hypersecretion
  - Chronic bronchitis

- Parenchyma destruction
  - Pulmonary emphysema
COPD pathogenesis

Epithelium

Mucus

Goblet cell hyperplasia

Mucus gland hyperplasia

Cholinergic nerve

Neutrophil

Monocyte

CD8+ cell

Emphysema

Inflammation

© 2013 Global Initiative for Chronic Obstructive Lung Disease
Normal airflow

Airway held open by alveolar attachment

Normal subject

Obstruction

Airflow limitation

Mucus

Hypersecretion

COPD

Disrupted alveolar attachment secretion

Mucosal inflammation & fibrosis

Airway obstruction caused by
• Loss of attachment
• Mucosal inflammation and fibrosis
• Mucus hypersecretion
Global Strategy for Diagnosis, Management and Prevention of COPD

Risk Factors for COPD (gene environment interaction)

**Genes**

**Exposure to particles**
- Tobacco smoke
- Occupational dusts, organic and inorganic
- Indoor air pollution from heating and cooking with biomass in poorly ventilated dwellings
- Outdoor air pollution

Lung growth and development
Gender
Age
Respiratory infections
Socioeconomic status
Asthma/Bronchial hyper-reactivity
Chronic Bronchitis

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Diagnosis of COPD

**SYMPTOMS**
- Shortness of breath
- Chronic cough
- Sputum

**EXPOSURE TO RISK FACTORS**
- Tobacco
- Occupation
- Indoor/outdoor pollution

**SPIROMETRY**
Required to establish diagnosis

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Clinical presentation of COPD

• **Dyspnea**
  Hallmark symptom of COPD & caused disability w seek med attention

• **Cough**
  First symptoms of COPD & miss percept as smoking cough

• **Sputum production**
  Regular sputum production for 3 mo or more in 2 consecutive years

• **Wheezing and chest tightness**
  Nonspecific and vary between day & not distinguished from asthma

• **Additional feature of severe disease**
  Weight loss, anorexia and psychiatric problems
Spirometry for COPD
Diagnosis and Classification of Severity

<table>
<thead>
<tr>
<th></th>
<th>FEV₁</th>
<th>FVC</th>
<th>FEV₁/FVC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>4.150</td>
<td>5.200</td>
<td>0.8</td>
</tr>
<tr>
<td>COPD</td>
<td>2.350</td>
<td>3.900</td>
<td>0.6</td>
</tr>
</tbody>
</table>
Diagnosis and Assessment

• A clinical diagnosis of COPD should be considered in any patient who has dyspnea, chronic cough or sputum production, and a history of exposure to risk factors for the disease.

• Spirometry is required to make the diagnosis; the presence of a post-bronchodilator $\text{FEV}_1/\text{FVC} < 0.70$ confirms the presence of persistent airflow limitation and thus of COPD.
Fixed $\text{FEV}_1/\text{FVC}$ ratio vs. 5% LLN for diagnosis airflow limitation in COPD

Potentially under-diagnosed

Lower limited normal of $\text{FEV}_1/\text{FVC}$ based reference equation

Potentially over-diagnosed

False negative

False positive

David M Mannino, A Sonia Buist, William M Vollmer Thorax 2007
Bronchodilator reversibility test
(Short term bronchodilator response)

Spirogram

Flow-volume curve

Normal
Volume dependent obstruction
Obstruction with reversibility

FEV₁ = forced expiratory volume in 1 second  TLC = total lung capacity  FVC = forced vital capacity
RV = residual volume  PEFR = peak expiratory flow rate  PIFR = peak inspiratory flow rate

Variable reversibility depending on bronchodilator agent test in COPD

Donohue JF. Therapeutic responses in asthma and COPD. Bronchodilators. Chest. 2004

- Ipatropium only (n = 91) 11.2%
- Salbutamol only (n = 222) 27.4%
- Both (n = 280) 34.6%
- Neither (n = 217) 26.8%

Reversibility test with short acting bronchodilator

↑12% and 200 ml of FEV₁
Physiologic differences between asthma and COPD

<table>
<thead>
<tr>
<th>Physiology</th>
<th>Asthma</th>
<th>COPD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elastic recoil</td>
<td>Normal</td>
<td>Decreased</td>
</tr>
<tr>
<td>Diffusion capacity ($DL_{CO}$)</td>
<td>Normal or increased</td>
<td>Decreased</td>
</tr>
<tr>
<td>Lung volume</td>
<td>Normal</td>
<td>Hyperinflation</td>
</tr>
<tr>
<td>Bronchodilator response</td>
<td>Flow-dominant ($FEV_1$ response)</td>
<td>Volume dependent ($FVC$ response)</td>
</tr>
</tbody>
</table>

Sciurba FC. Chest 2004; 126: 117-124
Bronchodilator reversibility testing

- Post bronchodilator FEV\(_1\) after 400 \(\mu\)g of salbutamol
- Definition of reversibility (ATS): Increase in FEV\(_1\) (\(\Delta\text{FEV}_1\)) more than 12% and 200 ml from baseline
- Definition of “NOT fully reversible”: the presence of post bronchodilator FEV\(_1\) <80% predicted together with an FEV\(_1\)/FVC <0.70

- Bronchodilator reversibility no longer recommended for:
  - Diagnosis of COPD and differentiate from asthma
  - Predicting response to long term bronchodilator or steroid
Different trend of lung function decline
The FEV$_1$ decline in COPD (Peto and Modina)

Fletcher et al. BMJ. 1977; 1:1645-1648
Denise Modina et al International Journal of COPD 2012:7 95–99
Static Lung volume (↓ IC and ↑ RV)

IC = TLC - ERV

Healthy normal

COPD

Flow (L/s)

Volume (L)

Actual

Predicted

TLC

RV

IC

Actual

Predicted

Healthy normal

COPD
Static Lung volume (↓IC and ↑RV)

IC = TLC - ERV

Lung volume (% predicted TLC)

Normal

COPD

TLC
EILV
EELV
IRV
TV
EELV
IC
Dynamic hyperinflation

**Normal**

- TLC
- RV
- IC
- EELV
- IRV

**COPD**

- TLC
- RV
- IC
- EELV
- Air Trapping During Exercise
- Dynamic Hyperinflation
Global Strategy for Diagnosis, Management and Prevention of COPD

Classification of Severity of Airflow Limitation in COPD*

In patients with $\text{FEV}_1/\text{FVC} < 0.70$:

<table>
<thead>
<tr>
<th>GOLD</th>
<th>Severity</th>
<th>FEV$_1$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>GOLD 1</td>
<td>Mild</td>
<td>$\geq 80%$ predicted</td>
</tr>
<tr>
<td>GOLD 2</td>
<td>Moderate</td>
<td>$50% \leq \text{FEV}_1 &lt; 80%$ predicted</td>
</tr>
<tr>
<td>GOLD 3</td>
<td>Severe</td>
<td>$30% \leq \text{FEV}_1 &lt; 50%$ predicted</td>
</tr>
<tr>
<td>GOLD 4</td>
<td>Very Severe</td>
<td>$\text{FEV}_1 &lt; 30%$ predicted</td>
</tr>
</tbody>
</table>

*Based on Post-Bronchodilator FEV$_1$
Spirometric classifications

- Undefined
- Mild
- Moderate
- Moderately severe
- Severe
- Very severe

FEV₁ predicted percentage

ERS 1995
ATS 1995
SPLF 1996
BTS 1997
GOLD 2001

GOLD 1
GOLD 2
GOLD 3
GOLD 4
Exercise performance
(Six-minute walk distance: 6-MWT)

American Thoracic Society

ATS Statement: Guidelines for the Six-Minute Walk Test

This official statement of the American Thoracic Society was approved by the ATS Board of Directors
March 2002

Am J Respir Crit Care Med; 2002, 166, 111–117
ข้าพเจ้าไม่มีเคยมีอาการไอเลย  ข้าพเจ้าไอตลอดเวลานะ
ข้าพเจ้าไม่มีเสมหะในปอดเลย  ปอดของข้าพเจ้าเต็มไปด้วยเสมหะ
ข้าพเจ้าไม่มีรู้สึกแน่นหน้าอกเลย  ข้าพเจ้ารู้สึกแน่นหน้าอกมาก
เมื่อข้าพเจ้าเดินขึ้นเนินหรือขึ้นบันไดหนึ่งชั้น  เมื่อข้าพเจ้าเดินขึ้นเนินหรือขึ้นบันไดหนึ่งชั้นข้าพเจ้ารู้สึกเหนื่อยหยอบ
ข้าพเจ้ารู้สึกกระฉับกระเฉง  ข้าพเจ้ารู้สึกอ่อนเพลีย

<table>
<thead>
<tr>
<th>COPD Assessment Test (CAT) score</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ข้าพเจ้าไม่มีเคยมีอาการไอเลย</strong></td>
</tr>
<tr>
<td><strong>ข้าพเจ้าไม่มีเสมหะในปอดเลย</strong></td>
</tr>
<tr>
<td><strong>ข้าพเจ้าไม่มีรู้สึกแน่นหน้าอกเลย</strong></td>
</tr>
<tr>
<td>เมื่อข้าพเจ้าเดินขึ้นเนินหรือขึ้นบันไดหนึ่งชั้น</td>
</tr>
<tr>
<td>ข้าพเจ้ารู้สึกกระฉับกระเฉง</td>
</tr>
<tr>
<td>ข้าพเจ้าไม่มีความมั่นใจที่จะออกไปนอกบ้านทั้งๆที่ปกติข้าพเจ้ามีปัญหา</td>
</tr>
<tr>
<td>ข้าพเจ้านอนหลับสนิท</td>
</tr>
<tr>
<td>ข้าพเจ้ารู้สึกกระตุกกระกระจะ</td>
</tr>
</tbody>
</table>
Modified Medical Research Council MMRC score คะแนนความรู้สึกเหนื่อย

ให้根据自己ความรู้สึกเลือกข้อใดข้อหนึ่ง

0 คุณไม่มีความรู้สึกเหนื่อยเลยแม้ต้องออกกำลังกายอย่างหนัก

1 คุณรู้สึกเหนื่อยเฉพาะเมื่อต้องเดินรีบๆ หรือเดินขึ้นที่สูงเล็กน้อยเท่านั้น

2 คุณเดินได้ช้ากว่าคนที่อายุใกล้เคียงกันเนื่องจากเหนื่อย หรือต้องหยุดเดินเพื่อพักหายใจ เมื่อเดินอยู่ในบ้าน

3 คุณต้องพักหายใจหลังเดินได้ระยะทาง 90 เมตร (100 หลา) หรือหลังเดินทางราบได้เพียง 2-3 นาที

4 คุณเหนื่อยเกินกว่าที่จะออกจากบ้านได้ หรือเหนื่อยเมื่อต้องไปเสื้อ หรือ ถอดเสื้อ
Assessment of Symptom (scores)

COPD Assessment Test (CAT):
An 8-item measure of health status impairment in COPD (http://catestonline.org)

Breathlessness Measurement using the Modified British Medical Research Council (mMRC) Questionnaire:
Relates well to other measures of health status and predicts future mortality risk

Clinical COPD Questionnaire (CCQ):
Self-administered questionnaire developed to measure clinical control in patients with COPD (http://www.ccq.nl)
The frequent exacerbator phenotype

Frequency/severity by GOLD Categories

<table>
<thead>
<tr>
<th>Category</th>
<th>% of patients</th>
<th>Hospitalised for exacerbation in yr 1</th>
<th>Frequent exacerbations (2 or more)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GOLD II</td>
<td>7</td>
<td>7</td>
<td>22</td>
</tr>
<tr>
<td>GOLD III</td>
<td>18</td>
<td>18</td>
<td>33</td>
</tr>
<tr>
<td>GOLD IV</td>
<td>33</td>
<td>33</td>
<td>47</td>
</tr>
</tbody>
</table>


p<0.01
Factors Associated With Exacerbation Frequency

Exacerbation During Previous Year
FEV1 (per 100 mL decrease)
SGRQ Score (per 4 point increase)
Positive History for Reflux/Heartburn
White Cell Count (per increase of 1000/mL)

Odds Ratio for ≥2 versus 0 Exacerbations

- Exacerbation During Previous Year: 5.72 (P<0.001)
- FEV1 (per 100 mL decrease): 1.11 (P<0.001)
- SGRQ Score (per 4 point increase): 1.07 (P<0.001)
- Positive History for Reflux/Heartburn: 2.07 (P<0.001)
- White Cell Count (per increase of 1000/mL): 1.08 (P=0.002)

N=2138

How to assess COPD severity?

• **Assess symptoms**
  
  Dyspnea and cough (MMRC questionnaires) COPD assessment test (CAT)

  Clinical COPD Questionnaire (CCQ)

• **Assess degree of airflow limitation using spirometry**
  
  Post bronchodilator FEV$_1$ (80%, 80-50%, 50-30% and <30% predicted)

• **Assess risk of exacerbations**
  
  Two or more exacerbations within the last year *or* an FEV$_1$ < 50 % of predicted value

  One or more hospitalizations for COPD exacerbation should be considered high risk

• **Assess co-morbidities**
  
  Cardiac disease, myopathy, osteoporosis and depression

(GOLD 2015)
Combined Assessment of COPD (GOLD 2014)
Symptoms and risks of COPD stratification

Risk (GOLD Classification of Airflow Limitation)

(A) mMRC 0-1 CAT < 10 CCQ < 1
(B) mMRC > 2 CAT > 10 CCQ ≥ 1
(C) mMRC 0-1 CAT < 10 CCQ < 1
(D) mMRC > 2 CAT > 10 CCQ ≥ 1

Risk (Exacerbation history)
0 or 1 exacerbations per year not leading to hospitalization
Low Risk (A or B)
Two or more exacerbations per year:
High Risk (C or D)

Symptoms
Dyspnea: mMRC scale
COPD symptoms: CAT score or CCQ

If GOLD 1 or 2 and only
(One or more hospitalizations for COPD exacerbations should be considered high risk.)

exacerbations per year
not leading to hospitalization
Low Risk (A or B)

exacerbations per year:
High Risk (C or D)

(One or more hospitalizations for COPD exacerbations should be considered high risk.)
Global Strategy for Diagnosis, Management and Prevention of COPD

Combined Assessment of COPD

When assessing risk, choose the **highest** risk according to GOLD grade or exacerbation history. One or more hospitalizations for COPD exacerbations should be considered high risk.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Characteristic</th>
<th>Spirometric Classification</th>
<th>Exacerbations per year</th>
<th>mMRC</th>
<th>CAT</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Low Risk Less Symptoms</td>
<td>GOLD 1-2</td>
<td>≤ 1</td>
<td>0-1</td>
<td>&lt; 10</td>
</tr>
<tr>
<td>B</td>
<td>Low Risk More Symptoms</td>
<td>GOLD 1-2</td>
<td>≤ 1</td>
<td>≥ 2</td>
<td>≥ 10</td>
</tr>
<tr>
<td>C</td>
<td>High Risk Less Symptoms</td>
<td>GOLD 3-4</td>
<td>≥ 2</td>
<td>0-1</td>
<td>&lt; 10</td>
</tr>
<tr>
<td>D</td>
<td>High Risk More Symptoms</td>
<td>GOLD 3-4</td>
<td>≥ 2</td>
<td>≥ 2</td>
<td>≥ 10</td>
</tr>
</tbody>
</table>

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ผู้ป่วยชายอายุ 72 ปี มาด้วยอาการเหนื่อยไอ และมีเสมหะมากได้ 2 เดือน
ประวัติปัจจุบัน มีอาการเหนื่อยโดยเฉพาะเวลาออกแรง ราว 3 เดือน
• ไอมีเสมหะมาได้ 2 ปี ไม่เคยรับการตรวจ หรือ ไม่เคยนอน รพ. มาก่อน
• มีประวัติสูบบุหรี่ยาเส้นมาได้ 40 ปีวันละ 20 มวน ปัจจุบันยังคงสูบ
• มีประวัติความดันโลหิตสูงมาได้ 5 ปี กินยา HCTZ (50) ½ tab OD
ตรวจร่างกาย
• Tachypnea มีการใช้กล้ามเนื้อ accessory muscle
• มี increase of anterior posterior diameter of chest
• ฟังปอดได้ poor air entry และมี expiratory rhonchi both lungs
• ไม่พบ clubbing
ภาพถ่ายรังสีปอดพบว่ามี air trapping (hyperinflation)
Severe obstructive ventilatory defect (FEV₁ 34% predicted) without improvement of FEV₁ after bronchodilator administration.

Moderate arterial hypoxemia

6MWT = 255 m  MMRC = 2  BMI 18 Kg/m²

ABG : pH 7.42  PaCO₂ 42  PO₂ 65  HCO₃ 27

<table>
<thead>
<tr>
<th>Spirometry</th>
<th>Predicted value</th>
<th>Pre-BD</th>
<th>Pre-BD% predicted</th>
<th>Post-BD</th>
<th>Post-BD% predicted</th>
<th>% change</th>
</tr>
</thead>
<tbody>
<tr>
<td>FVC (L) max</td>
<td>3.31</td>
<td>2.41</td>
<td>73</td>
<td>2.71</td>
<td>82</td>
<td>12</td>
</tr>
<tr>
<td>FEV₁</td>
<td>2.36</td>
<td>0.76</td>
<td>32</td>
<td>0.81</td>
<td>34</td>
<td>0%</td>
</tr>
<tr>
<td>FEV₁/FVC</td>
<td>0.32</td>
<td></td>
<td></td>
<td>0.30</td>
<td></td>
<td>5.6%</td>
</tr>
<tr>
<td>FEF 25-75%</td>
<td>2.50</td>
<td>0.22</td>
<td>9%</td>
<td>0.24</td>
<td>10%</td>
<td>9%</td>
</tr>
<tr>
<td>PEFR (L/s)</td>
<td>6.53</td>
<td>3.30</td>
<td>51%</td>
<td>3.00</td>
<td>46%</td>
<td>-9</td>
</tr>
</tbody>
</table>
Combined Assessment of COPD

Use combined assessment

Patient is now in 1 of 4 categories:

A: Less symptoms, low risk
B: More symptoms, low risk
C: Less symptoms, high risk
D: More symptoms, high risk

Symptoms
(mMRC or CAT score or CCQ)

Risk
(GOLD Classification of Airflow Limitation)

Risk
(Exacerbation history)

mMRC 0-1
CAT < 10

mMRC ≥ 2
CAT ≥ 10

(A) (B) (C) (D)

GOLD 2013
COPD patients are at increased risk for:

- Cardiovascular diseases
- Osteoporosis
- Respiratory infections
- Anxiety and Depression
- Diabetes
- Lung cancer
- Bronchiectasis

These comorbid conditions may influence mortality and hospitalizations and should be looked for routinely, and treated appropriately.
GOLD 2015 summary
COPD multidimensional assessment

Assess symptoms
- COPD Assessment Test (CAT)
- Modified Medical Research Council Breathlessness scale (mMRC)

Assess degree airflow limitation
- Spirometric classification airflow limitation:
  - GOLD 1 (Mild; FEV₁ ≥ 80% predicted)
  - GOLD 2 (Moderate; FEV₁ < 80% predicted)
  - GOLD 3 (Severe; FEV₁ < 50% predicted)
  - GOLD 4* (Very severe; FEV₁ < 30% predicted)

Assess risk of exacerbations
- History of exacerbations AND Spirometry
  - FEV₁ < 50% or ≥ 2 exacerbations within the last year are indicators of high risk
  - One or more hospitalizations for COPD exacerbation should be considered high risk.

Assess co-morbidities
- Co-morbidities should be actively looked for and treated appropriately
- Most frequent co-morbidities are cardiovascular disease, depression and osteoporosis
ผู้ป่วย HN 390856

• ท่านให้การวินิจฉัยว่าเป็นโรคปอดอุดกั้น
COPD (chronic bronchitis and emphysema )
Severe symptoms (MMRC 2)
Stage (severe) : FEV₁ Post bronchodilator 30-50% (GOLD 3)
GOLD D COPD
Current smoking
Co-morbid Hypertension

• ท่านให้การรักษาอย่างไร
Bronchodilator therapy inhaled/oral (prn or regular)
Inhaled corticosteroid ± LABA ± LAMA
Mucolytics
Pulmonary rehabilitation
Smoking cessation
Vaccination
Manage Stable COPD: Goals of Therapy

- Relieve symptoms
- Improve exercise tolerance
- Improve health status
- Prevent disease progression
- Prevent and treat exacerbations
- Reduce mortality

Reduce symptoms
Reduce risk
<table>
<thead>
<tr>
<th>Therapeutic Options: COPD Medications</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Beta$_2$-agonists</strong></td>
</tr>
<tr>
<td>Short-acting beta$_2$-agonists (SABA)</td>
</tr>
<tr>
<td>Long-acting beta$_2$-agonists (LABA)</td>
</tr>
<tr>
<td><strong>Anticholinergics (antimuscarinic drugs)</strong></td>
</tr>
<tr>
<td>Short-acting anticholinergics (SAMA)</td>
</tr>
<tr>
<td>Long-acting anticholinergics (LAMA)</td>
</tr>
<tr>
<td><strong>Combination short-acting beta$_2$-agonists + anticholinergic in one inhaler</strong></td>
</tr>
<tr>
<td>Methylxanthines</td>
</tr>
<tr>
<td>Inhaled corticosteroids</td>
</tr>
<tr>
<td><strong>Combination long-acting beta$_2$-agonists + corticosteroids in one inhaler</strong></td>
</tr>
<tr>
<td>Systemic corticosteroids</td>
</tr>
<tr>
<td>Phosphodiesterase-4 inhibitors</td>
</tr>
</tbody>
</table>
Different bronchodilator in asthma and COPD

<table>
<thead>
<tr>
<th>Asthma</th>
<th>COPD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Short acting β2 agonist</strong></td>
<td><strong>Short acting β2 agonist s</strong></td>
</tr>
<tr>
<td>-Dosed as needed</td>
<td>-Regularly dosed</td>
</tr>
<tr>
<td>-tolerance</td>
<td>-No tolerance</td>
</tr>
<tr>
<td><strong>Long acting β2 agonist</strong></td>
<td><strong>Long acting β2 agonist s</strong></td>
</tr>
<tr>
<td>-Monotherapy associated with increase frequency of exacerbation</td>
<td>-Monotherapy associated with decrease frequency of exacerbation</td>
</tr>
<tr>
<td></td>
<td>-Little tolerance</td>
</tr>
<tr>
<td><strong>Anticholinergics</strong></td>
<td><strong>Anticholinergics</strong></td>
</tr>
<tr>
<td>-added on therapy in severe asthma</td>
<td>-efficacious in acute and stable disease</td>
</tr>
<tr>
<td>-Efficacious in acute asthma attack</td>
<td></td>
</tr>
</tbody>
</table>

Bronchodilators effect airflow limitation by targeting broncho-constriction & reducing air trapping.

- **Air trapping**
- **Bronchoconstriction**

**Smooth muscle relaxation**

- Reduced hyperinflation
- Improved respiratory muscle function
- Increased mucociliary clearance

- **β2- agonist** (SABA and LABA)
- **Anticholinergic or anti-muscarinic agent** (SAMA and LAMA)
- **Methylxanthine** (SR theophylline)
Inhaled bronchodilator categories

- **Duration of action**
  - Short acting (~4 hours)
  - Long acting (~12 hours)

- **Mechanisms of action**
  - β2 adrenoreceptor (Increase c AMP formation)
  - Muscarinic receptor antagonist
    (Antagonize constricting effect of Ach on airway smooth muscle)

- Providing the effective symptomatic relief
- First line therapy of choice for airway obstruction
- Long-acting bronchodilators (versus short-acting)

More effective & more convenient
Therapeutic Options: Bronchodilators

- Long-acting inhaled bronchodilators are convenient and more effective for symptom relief than short-acting bronchodilators.
- Long-acting inhaled bronchodilators reduce exacerbations and related hospitalizations and improve symptoms and health status.
- Combining bronchodilators of different pharmacological classes may improve efficacy and decrease the risk of side effects compared to increasing the dose of a single bronchodilator.
The present and the future of LAMA/LABA

**LAMA**
- Tiotropium
- Glycopyronium
- Umeclidinium bromide
- Aclidinium bromide

**LABA**
- Oladaterol
- Indacaterol
- Vilanterol
- Carmoterol
- Formoterol
- Salmeterol
LABA/LAMA synergy
Potential intracellular signaling pathway

Effector
- LABA
- Ach
- LAMA

Receptor
- β2
- M2
- M3

Downstream Effect
- Adenylyl cyclase
- ↑c-AMP (Relaxation)
- ↑Ca^{2+} (Contraction)  
  Endoplasmic reticulum

PDE inhibitors

• **Non selective PDE inhibitors**
  - Theophylline
  - Doxofylline (novofylline)

• **Selective PDE4 inhibitors**
  - Rolipram
  - Cilomilast
  - Roflumilast (and Roflumilast N-oxide)
  - Piclamilast
Dual mechanisms of theophylline

- **B2 agonist** and **Adenyl cyclase**
  - **B2 receptors**
  - ATP → Cyclic 3,5 AMP → 5-AMP → Phosphodiesterase (PDE) → Broncho dilatation

- **Theophylline**
  - **Adenosine receptors**
  - Adenosine
  - Bronchoconstriction Mediator release
  - Theophylline

Joseph L Rau Textbook of Respiratory Pharmacology 7th edition
Therapeutic Options: Theophylline

- Theophylline is less effective and less well tolerated than inhaled long-acting bronchodilators and is not recommended if those drugs are available and affordable.

- There is evidence for a modest bronchodilator effect and some symptomatic benefit compared with placebo in stable COPD. Addition of theophylline to salmeterol produces a greater increase in FEV₁ and breathlessness than salmeterol alone.

- Low dose theophylline reduces exacerbations but does not improve post-bronchodilator lung function.
# Comparison PDE4 inhibitors and theophyline

<table>
<thead>
<tr>
<th>Properties</th>
<th>PDE4 inhibitors</th>
<th>Theophyline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mechanism of action</td>
<td>Suppression of PDE4 enzyme (A-D)</td>
<td>Adenosine receptor antagonism (A₁ and A₂)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HDAC activity stimulation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Weak unspecific PDE inhibition</td>
</tr>
<tr>
<td>Cardiac and neurologic safety</td>
<td>Cardiac and neurologic safety proved (roflumilast)</td>
<td>Adverse event cause by adenosine antagonism (seizer and arrhythmia)</td>
</tr>
<tr>
<td>Gastrointestinal side effect</td>
<td>Common (&gt;10%)</td>
<td>Nausea and acid production</td>
</tr>
<tr>
<td>Weight loss</td>
<td>Common (&gt;2 kg)</td>
<td>Less common</td>
</tr>
<tr>
<td>Drug and food interaction</td>
<td>No known</td>
<td>Drugs (ciemetidine, phenytoin, rifampicin fluconazole) &amp; high protein diet (increase clearance)</td>
</tr>
<tr>
<td>Effect of smoking</td>
<td>Sustained plasma level &amp; efficacy in smokers</td>
<td>Increase clearance</td>
</tr>
<tr>
<td>Plasma level monitoring</td>
<td>Not necessary</td>
<td>Obligatory</td>
</tr>
<tr>
<td>Rebound effect after withdraw</td>
<td>No</td>
<td>Rebound of lung function decrease 32 hrs</td>
</tr>
</tbody>
</table>
Summary

Different bronchodilator mechanisms

- **Beta receptor (B2 agonist)**
  - SABA, LABA
  - Cyclic AMP
  - PDE

- **Anticholinergic**
  - LAMA, SAMA
  - ACh

- **Theophylline**

Airway smooth muscle
### ICS Pharmacology

<table>
<thead>
<tr>
<th>Inhaled steroid</th>
<th>Relative receptor affinity</th>
<th>Protein binding (%)</th>
<th>Bioavailability (%)</th>
<th>Clearance (L/min)</th>
<th>Volume distribution (L/kg)</th>
<th>Water solubility (μg/mL)</th>
<th>Half-life (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Oral</td>
<td>Pulmonary</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beclomethasone</td>
<td>0.5/13</td>
<td>87</td>
<td>15-20/26-40</td>
<td>50-60</td>
<td>150/120</td>
<td>ND</td>
<td>0.1/10</td>
</tr>
<tr>
<td>Budesonide</td>
<td>9.4</td>
<td>88</td>
<td>11</td>
<td>15-30</td>
<td>84</td>
<td>2.7-4.3</td>
<td>14</td>
</tr>
<tr>
<td>Ciclesonide</td>
<td>0.12</td>
<td>99</td>
<td>&lt;1</td>
<td>50</td>
<td>152</td>
<td>200</td>
<td>14</td>
</tr>
<tr>
<td>Flunisolide</td>
<td>1.9</td>
<td>ND</td>
<td>21</td>
<td>ND</td>
<td>ND</td>
<td>1.8</td>
<td>100</td>
</tr>
<tr>
<td>Fluticasone</td>
<td>18.0</td>
<td>90</td>
<td>&lt;1</td>
<td>29</td>
<td>0.9-1.3</td>
<td>3.7-8.9</td>
<td>4</td>
</tr>
<tr>
<td>Mometasone</td>
<td>23</td>
<td>99</td>
<td>&lt;1</td>
<td>11</td>
<td>53</td>
<td>332</td>
<td>ND</td>
</tr>
<tr>
<td>Triamcinolone</td>
<td>3.6</td>
<td>2</td>
<td>23</td>
<td>ND</td>
<td>7</td>
<td>2</td>
<td>40</td>
</tr>
</tbody>
</table>
AECOPD reduction with ICS

Reduction of AE COPD is seen in more severe COPD (FEV1 < 50% predicted)

RR of AECOPD in COPD patients treated with ICS vs. placebo

- Vesbo
- Bourbeau
- Paggiaro
- Weir

Increased efficacy of ICS

Sin D JAMA 2003
ICS recommendation in COPD guidelines

- **CTS**: moderate to severe COPD who have recurrent acute exacerbations (i.e. 3 exacerbations or more per year, especially those requiring the use of oral steroid (Level 1)

- **GOLD**: for symptomatic COPD patient with FEV$_1$ <50% predicted and repeated exacerbation (for example 3 in the last three years) (Evidence A)

- **ATS/ ERS**: in patients with more advanced disease (FEV$_1$ < 50% predicted)

- **NICE**: for patients with an FEV$_1$ <50% predicted who are having 2 more exacerbation requiring treatment with antibiotics or oral steroid in a 12 month period. The aim of treatment is to reduce exacerbation rate and slow decline in health status
**SCF vs. SM**

**Effect on Exacerbations**
*(One-Year Data)*

Exacerbation Rates (per year)

- **SAL 50**: Salmeterol (50 mcg)
  - N = 385
  - 1.53

- **FSC 250/50**: Fluticasone (250 mcg) + salmeterol (50 mcg)
  - N = 391
  - 1.06

* * P < 0.001

**30.5% Reduction**

**SFC vs. SM vs. FP**

Reduces exacerbations
*3 years (TORCH)*

Annualised exacerbation rate

- **Placebo**: 1.13
- **Sal**: 0.97
- **FP**: 0.93
- **SFC**: 0.85

SFC vs placebo: 25% (p<0.001)
SFC vs salmeterol: 12% (p=0.002)
SFC vs FP: 9% (p=0.02)

**Comparison RX effect**

- Placebo vs salmeterol: 12%
- Placebo vs FP: 9%
- Placebo vs SFC: 25%


**Calverley PMA et al. N Eng J Med 2007; 356: 775-789.**
## TORCH: Adverse Events

<table>
<thead>
<tr>
<th>Annual Event Rate (≥0.05 in any group)*</th>
<th>Placebo (N=1,544)</th>
<th>Salmeterol (N=1,542)</th>
<th>Fluticasone (N=1,552)</th>
<th>Combination (N=1,546)</th>
</tr>
</thead>
<tbody>
<tr>
<td>COPD Exacerbation</td>
<td>0.92</td>
<td>0.76</td>
<td>0.78</td>
<td>0.67</td>
</tr>
<tr>
<td>URTI</td>
<td>0.10</td>
<td>0.08</td>
<td>0.09</td>
<td>0.11</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>0.09</td>
<td>0.09</td>
<td>0.10</td>
<td>0.10</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>0.04</td>
<td>0.04</td>
<td><strong>0.07</strong></td>
<td><strong>0.07</strong></td>
</tr>
<tr>
<td>Bronchitis</td>
<td>0.05</td>
<td>0.05</td>
<td>0.05</td>
<td>0.05</td>
</tr>
<tr>
<td>Headache</td>
<td>0.08</td>
<td>0.06</td>
<td>0.06</td>
<td>0.05</td>
</tr>
<tr>
<td>Candidiasis</td>
<td>0.02</td>
<td>0.02</td>
<td>0.09</td>
<td>0.07</td>
</tr>
</tbody>
</table>

| Percent of Patients                    |                   |                      |                       |                       |
|----------------------------------------|                   |                      |                       |                       |
| Pneumonia                              | 12.3              | 13.3                 | **18.3†**             | **19.6‡**             |
| Fractures                              | 5.1               | 5.1                  | 5.4                   | 6.3                   |
| Cataracts**                            | 21                | 15                   | 17                    | 27                    |

*Unless otherwise noted, **No cataracts at baseline, †P>0.001 between fluticasone and placebo, ‡P>0.001 between salmeterol+fluticasone and placebo as well as combination and salmeterol

## Landmark COPD studies

### TORCH versus UPLIFT

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>TORCH</th>
<th>UPLIFT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (yr)</td>
<td>65.1</td>
<td>65</td>
</tr>
<tr>
<td>Male sex (%)</td>
<td>77</td>
<td>75</td>
</tr>
<tr>
<td>Mean FEV\textsubscript{1} (L)</td>
<td>1.10</td>
<td>1.10</td>
</tr>
<tr>
<td>FEV\textsubscript{1} predicted</td>
<td>40.3%</td>
<td>39%</td>
</tr>
<tr>
<td>Reversibility of FEV\textsubscript{1}</td>
<td>3.6% ±3.7% of predicted</td>
<td>NA</td>
</tr>
<tr>
<td>Smoking history</td>
<td>47.7±27.1 pack-yr</td>
<td>49 pack-years</td>
</tr>
<tr>
<td></td>
<td></td>
<td>30% current smokers</td>
</tr>
<tr>
<td></td>
<td></td>
<td>70% former smokers</td>
</tr>
<tr>
<td>BMI</td>
<td>25.4±5.2</td>
<td>26</td>
</tr>
<tr>
<td>Exacerbation recall (hospitalization and/or antibiotics/oral steroids in the past year)</td>
<td>58%</td>
<td>NA</td>
</tr>
<tr>
<td>Use of other RS medication including ICS</td>
<td>49%</td>
<td>99%</td>
</tr>
<tr>
<td>COPD status</td>
<td>Mainly severe to very severe COPD (GOLD III-IV)</td>
<td>44.5% moderate (FEV\textsubscript{1} 50%-79% predict)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>44.8% severe (FEV\textsubscript{1} 30%-49% predict)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>10.7% very severe (FEV\textsubscript{1} &lt;30% predict)</td>
</tr>
</tbody>
</table>
## ICS-LABA combination in COPD trials

<table>
<thead>
<tr>
<th>ICS dose (mcg)</th>
<th>LABA dose (mcg)</th>
<th>Device</th>
<th>Duration (wks)</th>
<th>Authors (years)</th>
<th>Outcome measurement</th>
<th>Authors (years)</th>
<th>Outcome measurement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mometasone furoate 200, 400</td>
<td>Formoterol 10 mcg</td>
<td>MDI BID</td>
<td>52</td>
<td>Tashkin 2012</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Beclohexasone 200 mcg</td>
<td>Formoterol 12 mcg</td>
<td>MDI BID</td>
<td>48</td>
<td>Calverley 2010</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Budesonide 320, 160 mcg</td>
<td>Formoterol 9 mcg</td>
<td>MDI BID</td>
<td>48</td>
<td>Sharafkhaneh 2012</td>
<td>-</td>
<td>-</td>
<td>Yes</td>
</tr>
<tr>
<td>Fluticasone furoate 100, 50</td>
<td>Vilanterol 25 mcg</td>
<td>DPI OD</td>
<td>24</td>
<td>Kerwin 2013</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Fluticasone furoate 200, 100</td>
<td>Vilanterol 25 mcg</td>
<td>DPI OD</td>
<td>24</td>
<td>Martinez 2013</td>
<td>Yes</td>
<td>-</td>
<td>Yes</td>
</tr>
<tr>
<td>Fluticasone furoate 50, 200, 100</td>
<td>Vilanterol 25 mcg</td>
<td>DPI OD</td>
<td>4</td>
<td>Boscia 2012</td>
<td>Yes</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>
TORCH: Pneumonia incidence in COPD with increasing GOLD stage


**INSPIRE study**
Different type of COPD exacerbation

<table>
<thead>
<tr>
<th>Time to event (weeks)</th>
<th>Number at Risk</th>
<th>Rate ratio (CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SFC (n=658)</td>
<td>TIO (n=665)</td>
<td></td>
</tr>
<tr>
<td>0-13</td>
<td>666</td>
<td>1.28</td>
<td>1.32</td>
</tr>
<tr>
<td>13-26</td>
<td>560</td>
<td>0.69</td>
<td>0.85</td>
</tr>
<tr>
<td>26-39</td>
<td>531</td>
<td>0.97</td>
<td>0.82</td>
</tr>
<tr>
<td>39-52</td>
<td>510</td>
<td>1.19</td>
<td>1.19</td>
</tr>
<tr>
<td>52-65</td>
<td>494</td>
<td>0.97</td>
<td>0.97</td>
</tr>
<tr>
<td>65-78</td>
<td>476</td>
<td>0.814</td>
<td>0.814</td>
</tr>
<tr>
<td>78-91</td>
<td>456</td>
<td>0.97</td>
<td>0.97</td>
</tr>
<tr>
<td>91-104</td>
<td>445</td>
<td>1.19</td>
<td>1.19</td>
</tr>
</tbody>
</table>

**Probability of withdrawal prior to wk 104 (SFC 34.5% vs. TIO 41.7%)**

- **SFC vs Tio**: Cox’s hazard ratio 0.776 (95% CI 0.651, 0.926) p-value 0.005

**Number at Risk**
- SFC 50/500
- Tio 18

**Rate of all HCU exacerbations**
- SFC: 1.28 (1.21, 1.36)
- TIO: 1.32 (1.27, 1.37)
- Rate ratio: 0.97 (0.94, 1.01)

**HCU exacerbations using OCS**
- SFC: 0.69 (0.63, 0.76)
- TIO: 0.85 (0.80, 0.90)
- Rate ratio: 0.814 (0.74, 0.89)

**HCU exacerbations (ATB)**
- SFC: 0.97 (0.91, 1.02)
- TIO: 0.82 (0.76, 0.89)
- Rate ratio: 1.19 (1.02, 1.38)

**References**
**ICS/LABA vs. LABA Outcome: Pneumonia**

Analysis broken down by ICS/LABA type

<table>
<thead>
<tr>
<th>Study/ subgroup</th>
<th>Combination n/N</th>
<th>LABA n/N</th>
<th>Odds ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FLU/SAL</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mahler 2002</td>
<td>2/165</td>
<td>0/160</td>
<td>4.91 (0.23, 103.04)</td>
</tr>
<tr>
<td>SCO100470</td>
<td>2/518</td>
<td>4/532</td>
<td>0.51 (0.09, 2.81)</td>
</tr>
<tr>
<td>Hanania 2003</td>
<td>0/178</td>
<td>1/177</td>
<td>0.33 (0.01, 8.15)</td>
</tr>
<tr>
<td>TRISTAN</td>
<td>7/358</td>
<td>9/372</td>
<td>0.80 (0.30, 2.18)</td>
</tr>
<tr>
<td>O'Donnell 2006</td>
<td>0/62</td>
<td>0/59</td>
<td>Not estimable</td>
</tr>
<tr>
<td>Kardos 2007</td>
<td>23/507</td>
<td>7/487</td>
<td>3.26 (1.39, 7.67)</td>
</tr>
<tr>
<td><strong>TORCH</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ferguson 2008</td>
<td>29/394</td>
<td>15/388</td>
<td>1.98 (1.04, 3.75)</td>
</tr>
<tr>
<td>Anzueto 2009</td>
<td>26/394</td>
<td>10/403</td>
<td>2.78 (1.32, 5.84)</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>4122</td>
<td>4120</td>
<td>1.75 (1.25, 2.45)</td>
</tr>
</tbody>
</table>

Total events: 392 (Combination), 251 (LABA)
Heterogeneity: Tau² = 0.06; Chi² = 10.03, df = 7 (P = .19); I² = 30%
Test for overall effect: Z = 3.23 (P = .001)

| **BUD/FORM**   |                |          |                                |
| Calverley 2003 | 8/254          | 7/255    | 1.15 (0.41, 3.23)              |
| Tashkin 2008   | 10/558         | 5/284    | 1.02 (0.34, 3.01)              |
| Rennard 2009   | 37/988         | 17/495   | 1.09 (0.61, 1.96)              |
| **Subtotal (95% CI)** | 1800          | 1034     | 1.09 (0.69, 1.73)              |

Total events: 55 (Combination), 29 (LABA)
Heterogeneity: Tau² = 0.00; Chi² = 0.03, df = 2 (P = .99); I² = 0%
Test for overall effect: Z = 0.37 (P = .71)

<table>
<thead>
<tr>
<th>Total (95% CI)</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total</strong></td>
<td>5922</td>
<td>5154</td>
<td>1.55 [ 1.20, 2.01 ]</td>
</tr>
</tbody>
</table>

Total events: 447 (Combination), 280 (LABA)
Heterogeneity: Tau² = 0.04; Chi² = 12.84, df = 10 (P = 0.23); I² = 22%
Test for overall effect: Z = 3.32 (P = .0009)
Test for subgroup differences: Chi² = 2.62, df = 1 (P = .11), I² = 62%

---

Nannini et al. *Cochrane Database Syst Rev* 2012; 9: CD006829
Regular treatment with inhaled corticosteroids (ICS) improves symptoms, lung function and quality of life and reduces frequency of exacerbations for COPD patients with an FEV$_1$ < 60% predicted.

Inhaled corticosteroid therapy is associated with an increased risk of pneumonia.

Withdrawal from treatment with inhaled corticosteroids may lead to exacerbations in some patients.
Dose response curve for rate ratio of pneumonia in COPD
(Case control analysis)

Serious pneumonia event during the 5.4 years of follow-up

Fluticasone
RR 2.01
(1.93-2.10)

Budesonide
RR 1.17
(1.09-1.26)

Drug after deposition in the lungs?

(1) = first contact with airway surface liquid, (2) = absorption of active ingredients across pulmonary epithelium, this process is controlled mainly by physiochemical properties (dissolution rate and lipophilicity) (3) = clearance of non-dissolved particles by mucociliary clearance or phagocytosis

Ruge CA et al The Lancet / Respiratory Medicine (published online June 4th 2013)
## Adverse effects of ICS treatment in COPD (Types of evidence)

<table>
<thead>
<tr>
<th>Side effects</th>
<th>Randomized controlled trials</th>
<th>Observational studies</th>
<th>Systematic reviews</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumonia</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td></td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Bone fracture</td>
<td></td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Skin thinning &amp; bruising</td>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cataract</td>
<td></td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td></td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Oropharyngeal candidiasis</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

David Price et al Prim Care Respir J 2013
## COPD Pharmacologic treatments GOLD 2014

<table>
<thead>
<tr>
<th>Patient</th>
<th>Recommended first choices</th>
<th>Alternative choices</th>
<th>Other possible choices</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>SAMA prn</td>
<td>LAMA or</td>
<td>Theophylline</td>
</tr>
<tr>
<td></td>
<td>or</td>
<td>LABA or</td>
<td></td>
</tr>
<tr>
<td></td>
<td>SABA prn</td>
<td>SABA and SAMA</td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>LAMA</td>
<td>LAMA and LABA</td>
<td>SABA and/or SAMA or</td>
</tr>
<tr>
<td></td>
<td>or</td>
<td></td>
<td>SAMA or</td>
</tr>
<tr>
<td></td>
<td>LABA</td>
<td></td>
<td>Theophylline</td>
</tr>
<tr>
<td>C</td>
<td>ICS + LABA</td>
<td>LAMA and LABA</td>
<td>SABA and/or SAMA or</td>
</tr>
<tr>
<td></td>
<td>or</td>
<td>LAMA and PDE4-inh.</td>
<td>SAMA or</td>
</tr>
<tr>
<td></td>
<td>LAMA</td>
<td>LABA and PDE4 inh.</td>
<td>Theophylline</td>
</tr>
<tr>
<td>D</td>
<td>ICS + LABA</td>
<td>ICS + LABA and LAMA</td>
<td>Carbocysteine or</td>
</tr>
<tr>
<td></td>
<td>and/or</td>
<td>or</td>
<td>SABA and/or SAMA or</td>
</tr>
<tr>
<td></td>
<td>LAMA</td>
<td>LAMA and LABA</td>
<td>SAMA or</td>
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<td></td>
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<td>LAMA and PDE4-inh.</td>
<td>Theophylline</td>
</tr>
</tbody>
</table>

GOLD guideline 2014
Etiology, pathology and physiology

Obstructive airway diseases

Asthma
- Allergy
- Sensitization
- Th2 predominant
- Parenchyma not involved
- BSM enlarged in airway
- CD4+ (Th2), eosinophils, mast cells
- IL4, IL5, IL-13
- Small airway dysfunction

COPD
- Tobacco smoking
- Biomass exposure
- Irritants
- Parenchyma destruction
- Small airway fibrosis
- CD8+ neutrophils
- LTB4, TNF-α, CXCL-8

Airway inflammation
- MØ, CD3+ CD45+
- Lymphocytes
- IL4 LTB4
- Mucus secretion

Reversible
Airway obstruction
Partially reversible
What is asthma? What is COPD?

Asthma

• Airway hyperresponsiveness
• Recurrent episodes of symptoms
• Widespread and variable airflow obstruction that is reversible in nature

COPD

• Exacerbations and comorbidities
• Characterized by persistent airflow limitation and progressive disease associated with an enhanced chronic inflammatory response in the airways and the lung to noxious particles or gases

Global Initiative for Chronic Obstructive Lung Disease. 2013
Dutch hypothesis

Common cause?

Common mechanisms

Asthma  COPD

British hypothesis

Different causes

Different mechanisms

Asthma  COPD

COLD or CNSLD
### Step 1  Diagnosis Chronic Airway Disease

Do symptoms suggest chronic airway disease?

- **Yes**
- **No**

### Step 2  Syndromic Diagnosis in Adults

i) Assemble the features for asthma and COPD that best describe the patient

ii) Compare number of features in favor of each diagnosis and selected diagnosis

<table>
<thead>
<tr>
<th>Feature if present</th>
<th>Favors asthma</th>
<th>Favors 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 symptom</td>
<td>□ Variation over minutes, hrs of day □ Worse during night or early morning □ Triggered by exercise, emotions, dust or exposure to allergens</td>
<td>□ Persistent despite treatment □ Good and bad days but always daily symptoms and exertional dyspnea □ Chronic cough and sputum preceded onset of dyspnea, unrelated to triggers</td>
</tr>
<tr>
<td>Lung function</td>
<td>□ Record of variable airflow limitation (spirometry, peak flow)</td>
<td>□ Record of persistent airflow limitation (post-bronchodilator FEV$_1$/FVC &lt; 0.7)</td>
</tr>
</tbody>
</table>
## Step 2  Syndromic Diagnosis in Adults

i) Assemble the features for asthma and COPD that best describe the patient

ii) Compare number of features in favor of each diagnosis and selected diagnosis

<table>
<thead>
<tr>
<th>Feature if present</th>
<th>Favors asthma</th>
<th>Favors COPD</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFT b/w symptom</td>
<td>□ Normal</td>
<td>□ Abnormal</td>
</tr>
<tr>
<td>Past history or family history</td>
<td>□ Previous doctor DX of asthma</td>
<td>□ Previous doctor DX of COPD, chronic bronchitis or emphysema</td>
</tr>
<tr>
<td></td>
<td>□ Family history of asthma, and other allergic rhinitis or eczema</td>
<td>□ Heavy exposure to a risk factor: tobacco smoke, biomass fuels</td>
</tr>
<tr>
<td>Time course</td>
<td>□ No worsening of symptoms over time. Symptoms vary either seasonally, or from year to year</td>
<td>□ Symptoms slowly worsening over time (progressive course over years)</td>
</tr>
<tr>
<td></td>
<td>□ May improve spontaneously or have an immediate response to BD or ICS over wks</td>
<td>□ Rapid-acting bronchodilator treatment provides only limited relief</td>
</tr>
<tr>
<td>Chest X-ray</td>
<td>□ Normal</td>
<td>□ Severe hyperinflation</td>
</tr>
</tbody>
</table>

Note: these feature best distinguish B/W asthma and COPD. Several feature (3 or more) for either asthma or COPD suggest that diagnosis. If there is similar numbers for both asthma and COPD, consider diagnosis of ACOS.
**Step 1** Diagnosis Chronic Airway Disease

Do symptoms suggest chronic airway disease?

Yes

**Step 2** Syndromic Diagnosis in Adults

i) Assemble the features for asthma and COPD that best describe the patient

ii) Compare number of features in favor of each diagnosis and selected diagnosis

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Asthma</th>
<th>Some feature of asthma</th>
<th>Feature of both</th>
<th>Some feature of COPD</th>
<th>COPD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Confidence in diagnosis</td>
<td>Asthma</td>
<td>Possible asthma</td>
<td>Could be ACOS</td>
<td>Possible COPD</td>
<td>COPD</td>
</tr>
</tbody>
</table>

**Step 3** Perform spirometry

Marked reversible airflow limitation (pre post DB) or other proof of variable airflow limitation

<table>
<thead>
<tr>
<th>Step 4 Initial treatment</th>
<th>Asthma drug no LABA mono-Rx</th>
<th>Asthma drugs no LABA mono-Rx</th>
<th>ICS and LABA +/- LAMA</th>
<th>COPD drugs</th>
<th>COPD drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post BD FEV1/FVC &lt; 0.7</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Positions for COPD treatment
Phenotypic approach

Treatment of COPD by Clinical Phenotypes

- **A**: Emphysematous phenotype
- **B**: Chronic bronchitic phenotype
- **C**: Asthma/COPD Phenotype

Exacerbation frequency:
- 0-1/year
- >2/year

Airflow limitation by GOLD stage:
- 0
- 1
- 2
- 3
- 4

Symptoms (Questionnaire):

M. Miravitlles et al. Eur Respir J. 2013; 41(6)1252-6
2013 Global Initiative for Chronic Obstructive Lung Disease