A disease state characterized by the presence of airflow obstruction due to ✓ chronic bronchitis (and) or ✓ emphysema; the airflow obstruction is generally progressive, may be accompanied by airway hyperreactivity, and may be partially reversible.
**Pathogenesis of COPD**

- Noxious particles & gases
- Antioxidants
- Lung inflammation
- Antiproteinases
- Oxidative stress
- Proteinases
- COPD pathology

**Risk factors for COPD**

**Host factors**
- Gene (e.g., alpha-1 antitrypsin deficiency)
- Airway hyperresponsiveness
- Lung Growth

**Exposures**
- Smoking
- Occupational dusts and chemicals
- Air pollution
- Infections
- Asthma / bronchial hyperreactivity

**Aging Populations**

**Mechanism underlying airflow limitation in COPD**

- **INFLAMMATION**
  - Small airway disease
  - Airway inflammation
  - Airway remodeling
  - Parenchymal destruction
  - Loss of alveolar attachments
  - Decrease of elastic recoil

- **AIRFLOW LIMITATION**
  - Completely reversible
  - Airflow limitation
  - Completely irreversible
Key indicators for considering a Dx of COPD

- 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 FEV₁/FVC < 0.70 confirms the presence of persistent airflow limitation and thus of COPD.

Diagnosis of COPD

- Symptoms of COPD
  - Dyspnea: Progressive, persistent and worse with exercise.
  - Chronic cough: May be intermittent and may be unproductive.
  - Chronic sputum production: COPD patients commonly cough up sputum.
  - Spirometry: FEV₁/FVC ratio < 0.70 PLUS an FEV₁ < 80% predicted that is incompletely reversible with inhaled bronchodilator.
  - Absence of an alternative explanation for the symptoms and airflow limitation (Diff Dx)

Assess symptoms

- Clinical COPD Questionnaire (CCQ): Self-administered questionnaire developed to measure clinical control in patients with COPD (http://www.ccq.nl).
- Breathlessness Measurement using the Modified British Medical Research Council (mMRC) Questionnaire: relates well to other measures of health status and predicts future mortality risk.
mMRC (Modified Medical Research Council Dyspnea Score)

- Stage 0: No breathlessness
- Stage 1: Breathlessness on effort, e.g., climbing stairs or dressing
- Stage 2: Breathlessness on mild exertion, e.g., walking up a steep hill
- Stage 3: Breathlessness on walking at a normal pace, even on level ground
- Stage 4: Breathlessness at rest or on minimal exertion

CAT (COPD Assessment Test)

The CAT (COPD Assessment Test) is a 10-question tool to assess the impact of COPD on patients. Each question is scored on a scale of 1 to 5, with higher scores indicating greater impact. The total score ranges from 0 to 40, with scores:
- Less than 10: Minimal impact
- 10 or more: Moderate to severe impact

Global Strategy for Diagnosis, Management and Prevention of COPD

- Assess symptoms
- Assess degree of airflow limitation

Use spirometry for grading severity according to spirometry, using four grades split at 80%, 50% and 30% of predicted value.

Classification of severity of airflow limitation (based on postbronchodilator FEV₁)

In patients with FEV₁/FVC <0.70:
- **Stage I**: mild
  - FEV₁ ≥80% predicted
- **Stage II**: moderate
  - 50% ≤FEV₁ <80% predicted
- **Stage III**: severe
  - 30% ≤ FEV₁ < 50% predicted
- **Stage IV**: very severe
  - FEV₁ < 30% predicted
Assess symptoms
Assess degree of airflow limitation
Assess risk of exacerbations

Use history of exacerbations and spirometry.

- ≥ 2 exacerbations within the last year
- or an FEV₁ < 50% of predicted value are indicators of high risk.
- ≥ 1 hospitalization for a COPD exacerbation – high risk.

Assess risk of exacerbations next

If GOLD 3 or 4 or ≥ 2 exacerbations per year or ≥ 1 leading to hospital admission:
High Risk (C or D)

If GOLD 1 or 2 and only 0 or 1 exacerbations per year (not leading to hospital admission):
Low Risk (A or B)
Global Strategy for Diagnosis, Management and Prevention of COPD

Combined Assessment of COPD

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

CAT < 10
CAT ≥ 10
mMRC 0-1
mMRC 2-2

Assess COPD Comorbidities

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.

Differential Diagnosis: COPD and Asthma

COPD
- Onset in mid-life
- Symptoms slowly progressive
- Long smoking history

Asthma
- Onset early in life (often childhood)
- Symptoms vary from day to day
- Symptoms worse at night/early morning
- Allergy, rhinitis, and/or eczema also present
- Family history of asthma

Therapeutic Options: Key Points

- Smoking cessation has the greatest capacity to influence the natural history of COPD. Health care providers should encourage all patients who smoke to quit.
- All COPD patients benefit from regular physical activity and should repeatedly be encouraged to remain active.
### Therapeutic Options: Key Points

- Appropriate pharmacologic therapy can
  - reduce COPD symptoms
  - reduce the frequency and severity of exacerbations
  - improve health status and exercise tolerance.
- None of the existing medications for COPD has been shown conclusively to modify the long-term decline in lung function.

<table>
<thead>
<tr>
<th>Pharmacotherapies: Bronchodilators</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bronchodilator medications are central to the symptomatic management of COPD.</td>
</tr>
<tr>
<td>Bronchodilators are prescribed on an as-needed or on a regular basis to prevent or reduce symptoms.</td>
</tr>
<tr>
<td>The principal bronchodilator treatments are beta&lt;sub&gt;2&lt;/sub&gt;-agonists, anticholinergics, theophylline or combination therapy.</td>
</tr>
<tr>
<td>The choice of treatment depends on the availability of medications and each patient’s individual response in terms of symptom relief and side effects.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pharmacotherapies: Bronchodilators</th>
</tr>
</thead>
<tbody>
<tr>
<td>Long-acting inhaled bronchodilators are convenient and more effective for symptom relief than short-acting bronchodilators.</td>
</tr>
<tr>
<td>Long-acting inhaled bronchodilators reduce exacerbations and related hospitalizations improve symptoms and health status.</td>
</tr>
<tr>
<td>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.</td>
</tr>
</tbody>
</table>
**Bronchodilators: Theophylline**

- **Mode of action**: smooth muscle relaxation due to phosphodiesterase inhibition (PDE-IV), increases diaphragmatic contractility, may reduce inflammation.
- All studies that have shown efficacy of theophylline in COPD were done with slow-release preparations.
- Theophylline is less effective and less well tolerated than inhaled long-acting bronchodilators and is not recommended if those drugs are available and affordable.

**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.**

---

**Roflumilast – highly selective PDE₄ inhibitor**

- Theophylline – nonselective weak PDE inhibitor มีข้อจำกัด: safety and capability of drug absorbing.
- PDE-4 = subtype ของ PDE พบมากในบริเวณที่มีการอักเสบ และกล้ามเนื้อเรียบของทางเดินหายใจ การยับยั้ง PDE-4 แบบจำเพาะจะจำกัดที่ mast cells และ neutrophils.
- MOA: เพิ่มระดับของ cAMP โดยยับยั้งเอนไซม์ที่ทำลาย cAMP, ยับยั้ง mediator ที่ถูกเกิดการอักเสบทางเดินหายใจ.

**severe and very severe COPD (GOLD 3 and 4) and a history of exacerbations and chronic bronchitis**

**SE:** ปวดศีรษะ คลื่นไส้ ท้องเสีย สับสน
**Tiotropium bromide**

*Specific M1 and M3 Muscarinic Blockade*

- **Indication:** maintenance Tx of COPD
- **not suitable for relief of acute bronchospasm**
- **Side effects:**
  - Tiotropium, like ipratropium (quaternary ammonium compounds), is poorly absorbed from the GI tract and has very low systemic bioavailability. --- wide therapeutic margin
  - dryness of the mouth, a typical anticholinergic effect

---

**Tiotropium bromide**

- **GOLD guideline:** recommend for moderate or severe COPD use of regular tx of long acting bronchodilator, including tiotropium, rather than short acting bronchodilator
- tiotropium 18 mcg OD with or without salmeterol
- should not be use together with other ipratropium
- DPI (Handihaler)

---

**Tiotropium**

- 470 patients - stable COPD
- 3 month, randomized, double blind, once daily tiotropium vs. placebo

**Conclusions:**
- Increased FEV1 and FVC
- No tachyphylaxis
- Decreased rescue albuterol
- Decreased wheezing, SOB
- Dry mouth in 9.3%

Casaburi et al. CHEST 118:1294, 2000

**Tiotropium**

- 1207 patients, double blind, randomized trial,
- qd tiotropium vs. bid salmeterol vs. placebo

**Conclusions: Tiotropium**
- Fewer exacerbations
- Increased time to first exacerbation
- Fewer admissions
- Increased QOL

Tiotropium versus LABA for stable COPD

7 clinical studies totaling 12,223 patients with COPD
LABA: formoterol, salmeterol, indacaterol

Tiotropium was more effective than LABAs as a group in….
- preventing COPD exacerbations and disease-related hospitalisations
- no statistical differences between groups in overall hospitalisation rates or mortality during the study periods (3-12 months).

Inhaled Corticosteroids (ICS)

- Regular treatment with ICS:
  - improves symptoms, lung function and QoL
  - reduces frequency of exacerbations for COPD patients with an FEV$_1$ < 60% predicted.
  - ICS therapy is associated with an increased risk of pneumonia.

Combination: ICS + bronchodilator

- To reduce the frequency of exacerbation
  → ICS ให้ร่วมกับ LABA
  - more effective than the individual components in reducing exacerbations and improving LF
  - Combination therapy is associated with an increased risk of pneumonia.
  - LABA/ICS combination + tiotropium appears to provide additional benefits.

Meta-analysis: efficacy of ICS and LABA in a single inhaler with mono-component LABA alone in adults with COPD

14 trials involving 11,794 people with COPD

- ICS/LABA inhalers reduced (compared with their LABA component alone)
  - frequency of exacerbations an average of one exacerbation per year on a LABA to an average of 0.76 exacerbations per year on a combined inhaler.
  - risk of mortality was similar between the treatments
**Meta-analysis: efficacy of ICS and LABA in a single inhaler with mono-component LABA alone in adults with COPD**

- There was evidence of an overall increased risk of pneumonia with combined inhalers, from around 3/100 people/year on LABA to 4/100/year on combined inhalers.
- There was no significant difference between treatments in terms of hospitalisations.

**Systemic corticosteroids**

- From meta-analysis, patients with stable COPD who received oral corticosteroid had a mean FEV₁ > 20% improvement compared to placebo, 10%.

- Chronic treatment with systemic corticosteroids should be avoided (unfavorable benefit-to-risk ratio).

---

**Global Strategy for Diagnosis, Management and Prevention of COPD**

**Manage Stable COPD: Key Points**

- Identification and reduction of exposure to risk factors are important steps in prevention and treatment.
- Individualized assessment of symptoms, airflow limitation, and future risk of exacerbations should be incorporated into the management strategy.
- Pharmacologic therapy is used to reduce symptoms, reduce frequency and severity of exacerbations, and improve health status and exercise tolerance.

**Global Strategy for Diagnosis, Management and Prevention of COPD**

**Manage Stable COPD: Key Points**

- LABA and LAMA are preferred over short-acting formulations.
- Based on efficacy and side effects, inhaled bronchodilators are preferred over oral bronchodilators.
- Long-term treatment with ICS added to long-acting bronchodilators is recommended for patients with high risk of exacerbations.
Long-term monotherapy with OSC or ICS is not recommended in COPD.

The phosphodiesterase-4 inhibitor roflumilast may be useful to reduce exacerbations for patients with FEV$_1$ $<$ 50% of predicted, chronic bronchitis, and frequent exacerbations.

**Global Strategy for Diagnosis, Management and Prevention of COPD**

**Manage Stable COPD: Key Points**

- Influenza vaccines can reduce serious illness.
- Pneumococcal polysaccharide vaccine is recommended for COPD patients (≥65 years) and for COPD patients younger than age 65 with an FEV$_1$ < 40% predicted.
- The use of antibiotics other than for treating infectious exacerbations of COPD and other bacterial infections, is currently not indicated.
- Mucolytics: Patients with viscous sputum may benefit from mucolytics; overall benefits are very small.
- Antitussives: Not recommended.

**Global Strategy for Diagnosis, Management and Prevention of COPD**

**Therapeutic Options: Other Pharmacologic Treatments**

**Global Strategy for Diagnosis, Management and Prevention of COPD**

**Manage Stable COPD: Non-pharmacologic**

<table>
<thead>
<tr>
<th>Patient Group</th>
<th>Essential</th>
<th>Recommended</th>
<th>Depending on local guidelines</th>
<th>Other Possible Treatments</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Smoking cessation</td>
<td>Physical activity</td>
<td>Flu vaccination Pneumococcal vaccination</td>
<td></td>
</tr>
<tr>
<td>B, C, D</td>
<td>Smoking cessation Pulmonary rehabilitation</td>
<td>Physical activity</td>
<td>Flu vaccination Pneumococcal vaccination</td>
<td></td>
</tr>
</tbody>
</table>
The most common causes of COPD exacerbations are **viral upper respiratory tract infections** and infection of the tracheobronchial tree.

**SABA with or without SAMA** are usually the preferred bronchodilators for tx of an exacerbation.

**Systemic corticosteroids and antibiotics** can shorten recovery time, improve lung function and arterial hypoxemia ($\text{PaO}_2$), and reduce the risk of early relapse, tx failure, and length of hospital stay.

**Antibiotics** should be given to patients with:

- Three cardinal symptoms: increased dyspnea, increased sputum volume, and increased sputum purulence.
- Who require mechanical ventilation.

**Oxygen:** titrate to improve the patient’s hypoxemia with a target saturation of 88-92%.

#### Manage Exacerbations: Assessments

**Arterial blood gas measurements (in hospital):** with or without $\text{PaCO}_2 > 6.7$ kPa when breathing room air indicates respiratory failure.

- **Chest radiographs:** useful to exclude alternative diagnoses.
- **ECG:** may aid in the diagnosis of coexisting cardiac problems
- **Whole blood count:** identify polycythemia, anemia or bleeding.
- **Purulent sputum** during an exacerbation: indication to begin empirical antibiotic treatment.
- **Biochemical tests:** detect electrolyte disturbances, diabetes, and poor nutrition.
- **Spirometric tests:** not recommended during an exacerbation.

#### Summary

- Prevention of COPD is to a large extent possible and should have high priority.
- Spirometry is required to make the diagnosis of COPD; the presence of a post-bronchodilator $\text{FEV}_1/\text{FVC} < 0.70$ confirms the presence of persistent airflow limitation and thus of COPD.
- Combined assessment of symptoms and risk of exacerbations is the basis for non-pharmacologic and pharmacologic management of COPD.
- Treat COPD exacerbations to minimize their impact and to prevent the development of subsequent exacerbations.