Advances in the management of chronic obstructive lung diseases (COPD)

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University of Hong Kong
October, 2015
Chronic obstructive pulmonary disease (COPD)

- COPD in Hong Kong
- What is COPD?
- Implications of COPD in exacerbation
- Non-pharmacological measures
- Newer treatment strategy
Health care burden with COPD in HK

- The 5th cause of death
- Common particularly in elderly subjects (9% of elderly subjects age > 70)
- High disease burden (> 13,000 patients admitted with > 31,000 episodes every year)
- Overall ~8% medical bed days occupied
- 25% of unplanned re-admissions

1. M Chan-Yeung, Hong Kong Burden of Lung Diseases, Respirology 2008
2. Hong Kong Hospital Authority, 2012 - 13
Definition of COPD

- COPD, 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 comorbidities contribute to the overall severity in individual patients.
Mechanisms Underlying Airflow Limitation in COPD

**Small Airways Disease**
- Airway inflammation
- Airway fibrosis, luminal plugs
- Increased airway resistance

**Parenchymal Destruction**
- Loss of alveolar attachments
- Decrease of elastic recoil

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Pulmonary emphysema
Very severe airflow limitation

### Best Data

<table>
<thead>
<tr>
<th>Spirometry</th>
<th>Ref</th>
<th>Pre</th>
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<td>34</td>
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<td>Wash Time</td>
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### Diffusing Capacity (Hb 13.5)

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<th>Pre</th>
<th>% Ref</th>
<th>Post</th>
<th>% Ref</th>
<th>% Chg</th>
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<td>DLCO (mmol/kPa.min)</td>
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<td>1.5</td>
<td>32</td>
<td>4.6</td>
<td>1.5</td>
<td>32</td>
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<tr>
<td>DL Adj (mmol/kPa.min)</td>
<td>1.28</td>
<td>1.22</td>
<td>95</td>
<td>3.54</td>
<td>3.14</td>
<td>89</td>
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<tr>
<td>Kroghs K (1/min)</td>
<td>1.21</td>
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<td>IVC (Liters)</td>
<td>0.89</td>
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<td>F1 CH4 (%)</td>
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<td>F1 CO (%)</td>
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<td>0.300</td>
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<td>BHT (Sec)</td>
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</table>
Combined Assessment of COPD

- **Risk (GOLD Classification of Airflow Limitation)**
  - CAT < 10
  - Cats 1
  - Cats 2
  - Cats 3
  - Cats 4

- **Symptoms**
  - mMRC 0–1
  - mMRC > 2

- **Exacerbation History**
  - ≥ 1 leading to hospital admission
  - ≥ 2
  - or

- **Risk**
  - 1 (not leading to hospital admission)
  - 0 (admission)
If airflow obstruction is irreversible, can the disease course be modified?
Avoidance of risk factors

- smoking cessation
- reduction of indoor pollution
- reduction of occupational exposure

Influenza and pneumococcal vaccination
Smoking cessation has the greatest capacity to influence the natural history of COPD. Health care providers should encourage all patients who smoke to quit.

Pharmacotherapy and nicotine replacement reliably increase long-term smoking abstinence rates.

All COPD patients benefit from regular physical activity and should repeatedly be encouraged to remain active.
Decline of FEV1 with age and smoking habits

It’s never too late to quit
Is COPD treatable?
An exacerbation of COPD is:

“an acute event characterized by a worsening of the patient’s respiratory symptoms that is beyond normal day-to-day variations and leads to a change in medication.”
Exacerbations and worsening in health status over 3 years

ANOVA p<0.0003

SGRQ slope (units/yr)

Exacerbation Category

None in 3 years

Infrequent <1.65/yr

Frequent >1.65/yr

Getting worse faster

TORCH: Exacerbation rate and FEV$_1$ decline (all treatment arms)

Adjusted for smoking status, gender, baseline FEV$_1$, region, BMI, prior exacerbations, treatment, time, time by treatment and covariate by time
Exacerbation history is most powerful single predictor of exacerbations (independent of GOLD stage)
Increased risk of myocardial infarction and stroke following exacerbation of COPD

Annual rate of MI against the annual rate of exacerbation defined as prescription of steroids and antibiotics together. $\rho = 0.0131; \ P = .03$.

Data from 25,857 patients with COPD entered in The Health Improvement Network database over a 2-year period

2.27-fold (95% CI, 1.1-4.7; $P = .03$) increased risk of MI 1 to 5 days after exacerbation (defined by prescription of both steroids and antibiotics)

The most common causes of COPD exacerbations are viral upper respiratory tract infections and infection of the tracheobronchial tree.

Diagnosis relies exclusively on the clinical presentation of the patient complaining of an acute change of symptoms that is beyond normal day-to-day variation.

The goal of treatment is to minimize the impact of the current exacerbation and to prevent the development of subsequent exacerbations.
RESPIRATORY VIRUSES AND EXACERBATIONS

Up to 60% of COPD exacerbations associated with viruses
More often found in sputum than in nasal samples

Coinfection

Coronavirus
Chlamydia Pneumoniae
RSV Serology
Adenovirus
Parainfluenza
Influenza B
Influenza A
Rhinovirus

Seemungal et al Am J Respir Crit Care Med 2001
Seemungal et al ERJ 2000
Rohde Thorax 2003
Pneumococcal Vaccination

Cumulative Proportion of Patients Without Pneumonia

Log rank = 6.68
P = 0.0097

Time (days)

Vaccinated = 91
Control = 116

Log rank = 3.85
P = 0.0498 (NS)

Time (days)

Vaccinated = 132
Control = 114

Consequences of COPD Exacerbations

- Negative impact on quality of life
- Impact on symptoms and lung function
- Increased economic costs
- Accelerated lung function decline
- Increased Mortality
Are medications useful?
In what sense?
Appropriate pharmacologic therapy can reduce COPD symptoms, reduce the frequency and severity of exacerbations, and 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.

Influenza and pneumococcal vaccination should be offered depending on local guidelines.
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.
Accuhalers

Handihaler

Many others

LAMA + LABA = LAMA/LABA
• **SABA**: short-acting beta2-agonist
  
  *(salbutamol, albuterol)*

• **SAMA**: short-acting muscarinic antagonist
  
  *(ipratropium)*

• **LABA**: long-acting beta2-agonist
  
  *(indacaterol, vilanterol, salmeterol, formoterol)*

• **LAMA**: long-acting muscarinic antagonist
  
  *(tiotropium, glycopyrronium)*

• **ICS**: inhaled corticosteroids

• **PDE4I**: phosphodiesterase-4 inhibitor
  
  *(Roflumilast)*
Global Strategy for Diagnosis, Management and Prevention of COPD

Manage Stable COPD: Pharmacologic Therapy

RECOMMENDED FIRST CHOICE

GOLD 4
GOLD 3
GOLD 2
GOLD 1

Exacerbations per year

2 or more
≥1 leading to hospital admission

1 (not leading to hospital admission)

ICS + LABA
or
LAMA

ICS + LABA
and/or
LAMA

SAMA prn
or
SABA prn

LABA
or
LAMA

CAT < 10
mMRC 0-1

CAT ≥ 10
mMRC ≥ 2

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Global Strategy for Diagnosis, Management and Prevention of COPD

Manage Stable COPD: Pharmacologic Therapy

ALTERNATIVE CHOICE

C
LAMA and LABA
or
LAMA and PDE4-inh
or
LABA and PDE4-inh

D
ICS + LABA and LAMA
or
ICS + LABA and PDE4-inh
or
LAMA and LABA
or
LAMA and PDE4-inh.

GOLD 4
GOLD 3
GOLD 2
GOLD 1

A
LAMA
or
LABA
or
SABA and SAMA

B
LAMA and LABA

CAT < 10 mMRC 0-1
CAT ≥ 10 mMRC ≥ 2

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An inhaled corticosteroid combined with a long-acting beta\textsubscript{2}-agonist is more effective than the individual components in improving lung function and health status and reducing exacerbations in moderate to very severe COPD.

Combination therapy is associated with an increased risk of pneumonia.

Addition of a long-acting beta\textsubscript{2}-agonist/inhaled glucocorticosteroid combination to an anticholinergic (tiotropium) appears to provide additional benefits.
Muscarinic antagonist blocks \(M_3\) receptors \textbf{selectively} to prevent binding of acetylcholine.

- \(M_3\) family of muscarinic receptors are the ones primarily responsible for bronchoconstriction, whereas the
- \(M_2\) receptors are located in the heart and are involved in slowing heart rate following stimulation.
Long acting muscarinic agent (LAMA): Glycopyrronium bromide

- Randomized, double-blind, placebo-controlled, parallel-group, multi-center study, 52-week study.
- A total of 1066 patients were randomized to receive NVA237 (n=529), placebo (n=229) and open-label tiotropium (n=268).
Long acting muscarinic agent (LAMA): Glycopyrronium bromide

- NVA237 significantly **prolonged the time to first moderate or severe exacerbation** and reduced the rate of moderate or severe exacerbations over 52 weeks versus placebo, the results were comparable to those with open-label tiotropium 18 µg.
Inhalers therapy – LABA/LAMA/ICS
Some controversies?

- No evidence of cataracts, fractures or accelerated loss of BMD with ICS
- Dry mouth with LAMA, hoarse voice with ICS in low numbers
- No evidence of cardiac risk with beta-agonist
- Anticholinergic in mist format now found to be safe
- Use of ICS with increased pneumonia?
- But lower hospital mortality if on ICS
Can we do better?
Newer treatment options

- Treatment for co-morbidities – beta blockers can be used unless there is a clear asthmatic component (ACOS)
- Combinations of bronchodilators and/or ICS once daily
- PDE4 inhibition – roflumilast
COPD comorbidities

- Coronary artery diseases
- Congestive heart failure
- Atrial fibrillation
- Hypertension
- Diabetes
- Lung cancer
- Pneumonia
- Osteoporosis
- Anxiety
- Depression
**M2-111 and M2-112: Roflumilast reduces exacerbation rates**

**Study M2-111**

-14.0%  
(Cl -29;5)  
p=0.129

**Study M2-112**

-15.2%  
(Cl -30;2)  
p=0.085

**Post-hoc pooled analysis**

-14.3%  
(Cl -25;-2)  
p=0.026

*Exacerbations* per patient per year

<table>
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<tr>
<th>Study</th>
<th>Placebo</th>
<th>Roflumilast</th>
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<tr>
<td>M2-111</td>
<td>0.692</td>
<td>0.595</td>
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<td>M2-112</td>
<td>0.537</td>
<td>0.455</td>
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<tr>
<td>Post-hoc pooled</td>
<td>0.610</td>
<td>0.523</td>
</tr>
</tbody>
</table>

*Exacerbations* per patient per year:

- Placebo 0.692, Roflumilast 0.595 (Study M2-111)
- Placebo 0.537, Roflumilast 0.455 (Study M2-112)
- Placebo 0.610, Roflumilast 0.523 (Post-hoc pooled analysis)

**Notes:**
- Moderate or severe exacerbations treated with systemic steroids or leading to hospitalization or death.
Roflumilast efficacy is greatest in patients with chronic cough and sputum

- A post-hoc, pooled analysis of studies M2-111 and M2-112 examined the efficacy of roflumilast in exacerbation reduction in patient sub-groups

Overall
Current smokers
Former smokers
ICS: yes
ICS: no
Anticholinergic: yes
Anticholinergic: no
Very severe COPD
Severe COPD
Emphysema
Chronic bronchitis ± emphysema
Chronic bronchitis ± emphysema + ICS
Chronic bronchitis ± emphysema – ICS
Cough score ≥1
Cough score <1
Sputum score ≥1
Sputum score <1

ICS = inhaled corticosteroid.

Roflumilast can shift patients from the frequent to the more stable infrequent exacerbator state

- M2-124/125 pooled post-hoc analysis

**Frequent exacerbator subgroup**

The risk of *remaining* a frequent exacerbator was 20% lower in the roflumilast group

-20%

risk ratio=0.799; p=0.015

**Infrequent exacerbator subgroup**

The risk of *becoming* a frequent exacerbator was 23% lower in the roflumilast group

-23%

risk ratio=0.768; p=0.0018

*As-needed SABA and stable doses of LABAs/SAMAs were permitted. Concomitant ICS or LAMA use was not permitted.

Roflumilast was generally well tolerated in clinical studies

- Data were pooled from four 1-year placebo-controlled trials and four 6-month trials for evaluation of adverse reactions
- Adverse reactions that occurred with a frequency >2% of patients tested

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<tr>
<th>Adverse reaction</th>
<th>Roflumilast (N=4,438)</th>
<th>Placebo (N=4,192)</th>
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<tr>
<td>Diarrhoea, % (n)</td>
<td>9.5 (420)</td>
<td>2.7 (113)</td>
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<td>Weight loss, % (n)</td>
<td>7.5 (331)</td>
<td>2.1 (89)</td>
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<tr>
<td>Nausea, % (n)</td>
<td>4.7 (209)</td>
<td>1.4 (60)</td>
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<tr>
<td>Back pain, % (n)</td>
<td>3.2 (142)</td>
<td>2.2 (92)</td>
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<tr>
<td>Influenza, % (n)</td>
<td>2.8 (124)</td>
<td>2.7 (112)</td>
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<tr>
<td>Insomnia, % (n)</td>
<td>2.4 (105)</td>
<td>1.0 (41)</td>
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<tr>
<td>Decreased appetite, % (n)</td>
<td>2.1 (91)</td>
<td>0.4 (15)</td>
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Global Strategy for Diagnosis, Management and Prevention of COPD

Manage Stable COPD: Pharmacologic Therapy

RECOMMENDED FIRST CHOICE

<table>
<thead>
<tr>
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<th>GOLD 3</th>
<th>GOLD 2</th>
<th>GOLD 1</th>
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<tr>
<td>C</td>
<td>ICS + LABA or LAMA</td>
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<td>D</td>
<td>ICS + LABA and/or LAMA</td>
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<tr>
<td>A</td>
<td>SAMA prn or SABA prn</td>
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<tr>
<td>B</td>
<td>LABA or LAMA</td>
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Exacerbations per year

CAT < 10 mMRC 0-1
CAT ≥ 10 mMRC ≥ 2

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Global Strategy for Diagnosis, Management and Prevention of COPD

Manage Stable COPD: Pharmacologic Therapy

**ALTERNATIVE CHOICE**

**GOLD 4**
- LAMA and LABA
- LAMA and PDE4-inh

**GOLD 3**
- LAMA and LABA
- LABA and PDE4-inh

**GOLD 2**
- LAMA
- LABA
- SABA and SAMA

**GOLD 1**
- CAT < 10 mMRC 0-1
- CAT ≥ 10 mMRC ≥ 2

**Exacerbations per year**
- 2 or more
- ≥ 1 leading to hospital admission
- 1 (not leading to hospital admission)
- 0

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Dual bronchodilatation: LABA + LAMA

as a maintenance bronchodilator treatment to relieve symptoms in adult patients with chronic obstructive pulmonary disease (COPD).
Once daily dual bronchodilation

SPARK

- SPARK study provided evidence of the potential of dual bronchodilation as a future treatment option for patients with a history of exacerbations who require additional bronchodilation.

- Key inclusion criteria were post-bronchodilator forced expiratory volume in 1 second (FEV₁) of <50% of the predicted normal value, post-bronchodilator FEV₁/forced vital capacity (FVC) of <0.7, and a documented history of ≥1 COPD exacerbation in the previous 12 months requiring treatment with systemic corticosteroids and/or antibiotics.

**Figure 1. SPARK study design**

Multicenter, randomized, double-blind, parallel-group and active-controlled study

- Pre-randomization period
  - Pre-screening
  - Screening/run-in period
  - Day -21 to -15

- Double-blind treatment period
  - QVA149 110/50 μg o.d. via Breezhaler®
  - Glycopyrronium 50 μg o.d. via Breezhaler®
  - Open-label tiotropium 18 μg o.d. via Handihaler®
  - Day 1 to 448

- Variable double-blind treatment period
  - Day 448 to 532

*QVA149 and glycopyrronium were both double-blind treatments. Tiotropium was administered in an open-label fashion. o.d.—once-daily*

Once daily dual bronchodiilation

SPARK – clinical outcomes

Figure 3. Annual rates of all exacerbations

Values are mean rates with treatment differences expressed as RR (95% CI); **QVA149 vs glycopyronium: p=0.0012;

n=729  n=739  n=737

0.85**
(0.77, 0.94)

0.86**
(0.77, 0.94)

Figure 4. Least squares mean trough FEV₁ ± standard error

Differences between QVA149 and glycopyronium and tiotropium were statistically significant (p=0.0001) at each time point. Reproduced with permission from reference 7

Figure 5. Least squares mean (±standard error) SGRQ total scores


p-values for QVA149 vs glycopyronium: ***p<0.0001; **p=0.00049; *p=0.00042; **p=0.00076.
p-values for QVA149 vs tiotropium: ****p<0.00001; ***p=0.0001; **p=0.00037; *p=0.011.
Reproduced with permission from reference 7
Once daily dual bronchodilation

**LANTERN Study** - To evaluate the efficacy and safety of IND/GLY compared with SFC

Once daily dual bronchodilation

*LANTERN Study - To evaluate the efficacy and safety of IND/GLY compared with SFC*

IND/GLY significantly prolonged the time to first moderate or severe exacerbation by 31% compared with SFC.
Once daily dual bronchodilation

**LANTERN Study - To evaluate the efficacy and safety of IND/GLY compared with SFC**

Adverse events, serious adverse events, deaths and discontinuations was similar across the treatment groups

The incidence of pneumonia was 3-fold lower with IND/GLY compared with SFC

Pneumonia is a major risk associated with SFC and cause for hospitalization

<table>
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<th></th>
<th>IND/GLY n=372</th>
<th>SFC n=369</th>
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<tbody>
<tr>
<td><strong>Over all AEs</strong></td>
<td>149 (40.1)</td>
<td>175 (47.4)</td>
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<tr>
<td>Any AE events in ≥1.5% of any group</td>
<td></td>
<td></td>
</tr>
<tr>
<td>COPD worsening⁹</td>
<td>75 (20.2)</td>
<td>97 (26.3)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>30 (8.1)</td>
<td>45 (12.2)</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>13 (3.5)</td>
<td>26 (7.0)</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>7 (1.9)</td>
<td>4 (1.1)</td>
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<tr>
<td><strong>Pneumonia</strong></td>
<td>3 (0.8)</td>
<td>10 (2.7)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>2 (0.5)</td>
<td>6 (1.6)</td>
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<tr>
<td>Oropharyngeal pain</td>
<td>2 (0.5)</td>
<td>6 (1.6)</td>
</tr>
<tr>
<td>AEs leading to discontinuation</td>
<td>12 (3.2)</td>
<td>17 (4.6)</td>
</tr>
<tr>
<td>COPD worsening</td>
<td>3 (0.8)</td>
<td>7 (1.9)</td>
</tr>
<tr>
<td><strong>Any SAE</strong></td>
<td>20 (5.4)</td>
<td>35 (9.5)</td>
</tr>
<tr>
<td>COPD</td>
<td>6 (1.6)</td>
<td>17 (4.6)</td>
</tr>
<tr>
<td>SAEs leading to discontinuation</td>
<td>9 (2.4)</td>
<td>11 (3.0)</td>
</tr>
<tr>
<td>Non-SAE(s) leading to discontinuation</td>
<td>3 (0.8)</td>
<td>7 (1.9)</td>
</tr>
<tr>
<td><strong>Deaths</strong></td>
<td>2 (0.5)</td>
<td>0</td>
</tr>
</tbody>
</table>
Non-invasive ventilation (NIV) for COPD

NIV has assumed an important role in the management of acute respiratory failure (ARF).

Evidence is strong to support its use in ARF in patients with COPD exacerbations, acute cardiac pulmonary edema and obesity hypoventilation.

Appropriate patient selection and proper application of NIV is paramount in its success in improving patient outcomes and the efficiency of care.
Summary: Chronic obstructive pulmonary disease (COPD)

• Identification and reduction of exposure to risk factors.
• Individualized assessment of respiratory symptoms, airflow limitation, and risk of COPD exacerbations.
• COPD exacerbations are to be prevented
• Non-pharmacological measures, especially smoking cessation, vaccination and pulmonary rehabilitation training, bear significant impact on COPD management and prevention of exacerbation
• Long-acting bronchodilators +/- ICS to reduce symptoms, reduce frequency and severity of exacerbations, and improve health status and exercise tolerance.
Thank you
## COPD Assessment Test (CAT)

<table>
<thead>
<tr>
<th>Item</th>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I never cough</td>
<td>0 X 2 3 4 5</td>
<td>I cough all the time</td>
</tr>
<tr>
<td>I have no phlegm (mucus) in my chest at all</td>
<td>0 X 2 3 4 5</td>
<td>My chest is completely full of phlegm (mucus)</td>
</tr>
<tr>
<td>My chest does not feel tight at all</td>
<td>0 1 X 3 4 5</td>
<td>My chest feels very tight</td>
</tr>
<tr>
<td>When I walk up a hill or one flight of stairs I am not breathless</td>
<td>0 1 2 3 X 5</td>
<td>When I walk up a hill or one flight of stairs I am very breathless</td>
</tr>
<tr>
<td>I am not limited doing any activities at home</td>
<td>0 1 2 X 4 5</td>
<td>I am very limited doing activities at home</td>
</tr>
<tr>
<td>I am confident leaving my home despite my lung condition</td>
<td>0 1 2 3 X 5</td>
<td>I am not at all confident leaving my home because of my lung condition</td>
</tr>
<tr>
<td>I sleep soundly</td>
<td>0 1 X 3 4 5</td>
<td>I don’t sleep soundly because of my lung condition</td>
</tr>
<tr>
<td>I have lots of energy</td>
<td>0 1 2 3 X 4</td>
<td>I have no energy at all</td>
</tr>
</tbody>
</table>

**Total score** 22

**Scoring range 0-40**