Changing Landscapes in COPD
New Zealand Respiratory Conference

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Changing Landscapes in COPD: Summary

1. Overview of treatments available for COPD in NZ

2. The changing landscape of COPD
   • Summary of changes to the 2017 GOLD strategy update
   • FEV$_1$ for diagnosis and prognosis
   • Pharmacologic treatment updates - new place for LAMA/LABA
   • Patients most suitable for ICS/LABA

3. Non-pharmacological treatment for COPD
The changing landscape of COPD treatments in NZ

Introduction of new COPD therapies

### ICS/LABA

- **ICS/LABA**

### LAMA

- **LAMA**

### LAMA/LABA

- **LAMA/LABA**

Changes to 2017 GOLD Strategy Update

- **1 X new ICS/LABA** = Breo Ellipta
- **2 X new LAMA** = Incruse Ellipta and Spiriva in Respimat
- **3 X new dual LAMA/LABA bronchodilators** = Anoro Ellipta, Spiolto Respimat, Ultibro Breezhaler

* SPECIAL AUTHORITY REQUIREMENTS: LAMA monotherapy prior to LAMA/LABA

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LABAs have been left out to simplify schematic

ICS = inhaled corticosteroid; LABA = long acting beta2 agonist; LAMA = long acting muscarinic antagonist
Overview of inhalers available for COPD in NZ

Short-acting bronchodilators
- Respigen salbutamol
- Salamol salbutamol
- SalAir salbutamol
- Ventolin salbutamol
- Duolin salbutamol with ipratropium
- Bricanyl Turbuhaler terbutaline
- Atrovent ipratropium

ICS/LABA
- Onbrez Breezhaler indacaterol LABA (multiple strengths)
- Metrol salmeterol LABA
- Serevent Accuhaler salmeterol LABA
- Serevent salmeterol LABA
- Oxis Turbuhaler formoterol LABA
- Foradil formoterol LABA
- Seebri Breezhaler glycopyronium LAMA
- Spiriva Handihaler tiotropium LAMA
- Spiriva Respimat tiotropium LAMA
- Incruse Ellipta umeclidinium LAMA

ICS/LABA
- Symbicort Turbuhaler budesonide with formoterol (multiple strengths)
- Vannair budesonide with formoterol (multiple strengths)
- Breo Ellipta fluticasone with vilanterol (multiple strengths)
- FlexAir fluticasone with salmeterol (multiple strengths)
- Seretide Accuhaler fluticasone with salmeterol (multiple strengths)
- Seretide fluticasone with salmeterol (multiple strengths)

LAMA/LABA
- Ultibro Breezhaler glycopyronium with indacaterol LAMA/LABA
- Spiolto Respimat tiotropium with oxiseterol LAMA/LABA
- Anoro Ellipta umeclidinium with vilanterol LAMA/LABA


ICS = inhaled corticosteroid; LABA = long acting beta2 agonist; LAMA = long acting muscarinic antagonist
Changing landscapes in COPD

Summary of changes to the 2017 GOLD strategy update
Maintenance therapy for stable COPD: Where do we stand today?

We have clear treatment goals that have not changed

Reduce symptoms
- Relieve symptoms
- Improve exercise tolerance
- Improve health status

Reduce risk
- Prevent & treat exacerbations
- Prevent disease progression*
- Reduce mortality*

These goals should be achieved with minimal side effects

* To date, no pharmacotherapy has been proven to prevent disease progression or reduce mortality in COPD

Summary of changes to the 2017 GOLD strategy update - 1

- Lung function is no longer included in the treatment classification grid, but remains the **gold standard** for diagnosis and prognosis

- Greater emphasis on individualised treatment and individualised treatment choices – severity of symptoms and exacerbation history

- Greater guidance on treatment options, with escalation (and de-escalation) strategies now suggested – simplification in NZ

- Greater emphasis on the use of LAMA/LABA for appropriate patients
Summary of changes to the 2017 GOLD strategy update - 2

- Triple Therapy is recommended for patients who have a high burden of symptoms and/or exacerbations despite initial maintenance therapy.

- ICS/LABAs are recommended for patients (1) with co-existing asthma or ACOS, (2) with a higher blood eosinophil count, and (3) where patients are unable to access newer treatment classes (“treatable traits”).

- There is a significant relationship between poor inhaler technique and symptom control in patients with COPD; therefore, inhaler technique needs to be assessed regularly.

- Greater emphasis on exercise programmes, treatment of comorbid disease (CAD), and use of self management plans.

Changing landscapes in COPD

$FEV_1$ for diagnosis and prognosis (not treatment options)
Sub-phenotyping of older heavy smokers according to symptoms and lung function impairment (N=10,054).

Sub-phenotyping Criteria

**Group 1** (Healthy Smokers)
Asymptomatic
FEV1/FVC ≥ 70%, FEV1%p ≥ 80%

**Group 2** (GOLD 0)
Self-reported “Airways Disease”
FEV1/FVC ≥ 70%, FEV1%p all

**Group 3** (GOLD U)
“Asymptomatic”
FEV1/FVC ≥ 70%, FEV1%p < 80%

**Group 4** (Undiagnosed “COPD”)
“Asymptomatic”
FEV1/FVC < 70%, GOLD 1-4

**Group 5** (Diagnosed “COPD”)
Self-reported “Airways Disease”
FEV1/FVC < 70%, GOLD 1-4
Diagnosis

Assessment of airflow limitation (severity + prognosis)

Assessment of symptoms/risk of exacerbation

**NEW 2017 GOLD:** FEV$_1$ informs diagnosis and prognosis but not treatment recommendations

**FEV$_1$/FVC < 0.7**

<table>
<thead>
<tr>
<th>Grade</th>
<th>FEV$_1$ (%) pred.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>≥80</td>
</tr>
<tr>
<td>2</td>
<td>50-79</td>
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<tr>
<td>3</td>
<td>30-49</td>
</tr>
<tr>
<td>4</td>
<td>&lt;30</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Risk (Exacerbation history)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;2 OR &gt;1 leading to hospital admission</td>
</tr>
<tr>
<td>1, not leading to hospital admission</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Symptoms Breathlessness</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAT &lt;10 mMRC 0-1</td>
</tr>
<tr>
<td>CAT ≥10 mMRC ≥2</td>
</tr>
</tbody>
</table>

**FEV₁ is a poor predictor of individual disease severity**

Weak correlation between disease outcome parameters and FEV₁

- mMRC score: Rho = -0.36, p < 0.001
- SGRQ-C Total score: Rho = -0.38, p < 0.001
- 6MWD (Metres): Rho = -0.34, P < 0.001
- Number of exacerbations: Rho = -0.21, 0.001

GOLD 2011-2016: Patients stratified based on risk (airflow limitation + exacerbation history) and symptoms

Stratification to guide pharmacologic treatment algorithm

- **(C)**: high risk, less symptoms (GOLD Classification of Airflow Limitation)
- **(D)**: high risk, more symptoms
- **(A)**: low risk, less symptoms
- **(B)**: low risk, more symptoms

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

>2 OR
>1 leading to hospital admission
1, not leading to hospital admission
0

**Symptoms**

**Breathlessness**

NEW 2017 GOLD: Patients stratified based on risk (exacerbation history) and symptoms

Stratification to guide pharmacologic treatment algorithm

Assessment of symptoms: The CAT questionnaire (www.catestonline.org)

COPD Self-Assessment Test

Score/40
- mild 0-10
- mod 10-15
- severe 15-25
- very severe 25-40

Basis on which to establish
- overall disability
- specific disabilities and
- response to treatments

www.catestonline.org
## Assessment of symptoms: Modified MRC Breathlessness Score

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description of Breathlessness</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>I only get breathless with strenuous exercise.</td>
</tr>
<tr>
<td>1</td>
<td>I get short of breath when hurrying on level ground or walking up a slight hill.</td>
</tr>
<tr>
<td>2</td>
<td>On level ground, I walk slower than people of the same age because of breathlessness, or have to stop for breath when walking at my own pace.</td>
</tr>
<tr>
<td>3</td>
<td>I stop for breath after walking about 100 yards or after a few minutes on level ground.</td>
</tr>
<tr>
<td>4</td>
<td>I am too breathless to leave the house or I am breathless when dressing.</td>
</tr>
</tbody>
</table>

Changing landscapes of COPD

Overview of the new recommendations
Changes for Management of Stable COPD: Summary of new pharmacologic treatment algorithms by 2017 GOLD Update

A. Continue, stop or try alternative class of bronchodilator. Be sure to evaluate effect.

B. A long-acting bronchodilator (LABA or LAMA)

C. LAMA/LABA. Further exacerbation(s) lead to LABA/ICS.

D. LAMA/LABA/ICS. Consider rolumilast if FEV₁ <50% predicted and patient has chronic bronchitis. Consider macrolide if persistent symptoms/further exacerbations.

Risk (Increasing Exacerbations) 

Increasing Symptoms

Preferred treatment pathway=

‘Distilling’ the 2017 GOLD strategy update – NZ context

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**Diagram:**

- **Severe:** Partially reversible airflow limitation (>400 mL or >15%)
  - ACOS
    - LABA/ICS
  - LAM/LABA/ICS
- **Non-exacerbator:** Persistent symptoms/SOB and infrequent exacerbator
  - LABA/ICS
  - LAMA
- **Non-exacerbator:** Persistent symptoms/SOB and infrequent exacerbator
  - SABA
  - SABA+ICS
- **Severe:** Minimally reversible airflow limitation
  - LABA/ICS
  - LAMA
  - LAM/LABA/ICS

- **Non-exacerbator:** Frequent/recent exacerbator
  - LABA/ICS
  - LAMA
  - LAM/LABA/ICS

- **Non-exacerbator:** Late “irreversible” ACOS phase (>40 years old)
  - LABA/ICS
  - LAM/LABA
  - LAM/LABA/ICS

- **Non-exacerbator:** Early “reversible” asthma phase (<40 years old)
  - LABA/ICS
  - LAM/LABA
  - LAM/LABA/ICS

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**Step-up** (escalation) based on:
- Recent “exacerbation” or chest infection history
- Symptom score (CAT >10) or persistent SOB
- Low or highly variable expiratory flow rates (FEV₁ <50% or ±15% or ±400 mL)
- “High” blood serum eosinophil count (>300 µL⁻¹ or >4%)

**Step-down** (de-escalation/substitution if:
- Not ACOS
- No exacerbations or chest infections in last 1–2 years and stable dyspnoea
- Recent pneumonia (CXR confirmed) or other ICS-related complications
- “Low” blood serum eosinophil count (<300 µL⁻¹ or <4%)

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The 2017 GOLD strategy update
Group A: Low level of symptoms and low risk of exacerbation

Stratification to guide pharmacologic treatment algorithm

A bronchodilator

Evaluate effect

Continue, stop or try alternative class of bronchodilator

A long-acting bronchodilator (LABA or LAMA)

Increasing Symptoms

Preferred treatment pathway=

Group A: Low symptom level and low risk of exacerbation
Short-acting and long-acting mono-bronchodilators available in NZ


ICS = inhaled corticosteroid; LABA = long acting beta2 agonist; LAMA = long acting muscarinic antagonist
Changing landscapes of COPD

New place for LAMA/LABA
The 2017 GOLD strategy update
Group B: High level of symptoms and low risk of exacerbation

Stratification to guide pharmacologic treatment algorithm

A SAMA and/or SABA bronchodilator or long-acting bronchodilator (LAMA or LABA)

B Persistent symptoms

C Evaluate effect

D Consider rolumilast if FEV$_1$ <50% predicted and patient has chronic bronchitis

Preferred treatment pathway=

The 2017 GOLD strategy update

Group C: Low level of symptoms and high risk of exacerbation

Stratification to guide pharmacologic treatment algorithm

A bronchodilator

Evaluate effect

Continue, stop or try alternative class of bronchodilator

A long-acting bronchodilator (LABA or LAMA)

Persistent symptoms

Consider rolumilast if FEV₁ <50% predicted and patient has chronic bronchitis

Consider macroline

LAMA/LABA/ICS

ICS/LABA

LAMA/LABA

Further exacerbation(s)

LAMA

Further exacerbation(s)

LAMA/LABA

ICS/LABA

LAMA/LABA

ICS/LABA

Risk (Increasing Exacerbations)

Increasing Symptoms

Preferred treatment pathway=

Recent Key Trials in COPD Management

**AFFIRM/FLAME** – RCT showing non-inferiority (superiority) for LABA/LAMA vs LABA/ICS for improving FEV1, reducing symptoms and preventing exacerbations

**WISDOM** – withdrawal study showing substituting LABA/ICS with LABA/LAMA made no difference to exacerbations

**SUMMIT** – RCT showing LABA/ICS did not reduce cardiovascular mortality in high risk COPD patients (use aspirin and statins) but did help reduce FEV1 decline vs LABA alone – **quitting smoking and ↓exacerbations**
Anoro Ellipta (LABA/LAMA) demonstrates significant improvement of trough FEV\textsubscript{1} compared with monotherapy and placebo.

Anoro Ellipta (LABA/LAMA) significantly improved trough FEV$_1$ compared with tiotropium

Immediate, sustained, significant improvement in trough FEV$_1$

Results of 24-week, randomised, double-dummy, active-controlled, blinded, multi-centre, parallel-group studies that compared the efficacy and safety of Anoro Ellipta with tiotropium in subjects with COPD.

Changing landscapes in COPD

Patients most suitable for ICS/LABA
The 2017 GOLD strategy update
Group C: Low level of symptoms and high risk of exacerbation

Stratification to guide pharmacologic treatment algorithm

Preferred treatment pathway = 

Which of my COPD patients would benefit from an ICS?

GOLD 2017 recommendations:
In GOLD D patients, ICS/LABA as initial therapy may be the first choice in:
- Those patients who may co-existing asthma or a history and/or findings that are suggestive of asthma-COPD overlap syndrome
- Patients with high eosinophil counts may also be considered as a parameter to support the use of ICS-containing therapy

ACOS subgroup of COPD spectrum

• Recommendations are based on expert opinion and not RCTs (ACOS usually excluded from COPD trials)

• Features of ACOS
  – History of asthma (childhood or 20+ years of asthma) and smoking
  – History of atopy, allergic rhinitis or high IgE
  – High serum eosinophilia (>2%)
  – Highly variable PEFR or FEV$_1$ (>15% variability)

• About 20% of all COPD cohorts, suffer frequent exacerbations, moderate-severe GOLD grade (GOLD phenotype C and D)

• Assumed to
  – Gain greater benefit from ICS use with reduction in exacerbations
  – Have greater responsiveness to ICS with regards bronchodilator benefits
The effect of adding fluticasone furoate to vilanterol (Breo Ellipta) by blood eosinophils

The 2017 GOLD strategy update

Group D: High level of symptoms and high risk of exacerbation

Stratification to guide pharmacologic treatment algorithm

A bronchodilator

Evaluate effect

Continue, stop or try alternative class of bronchodilator

A bronchodilator

LAMA/LABA

LABA/ICS

LAMA/LABA

LAMA

LAMA/LABA/ICS

ICS/LABA

LAMA

LABA

LABA/ICS

ICS/LABA

Further exacerbation(s)

LAMA

LABA

LABA/ICS

ICS/LABA

Further exacerbation(s)

Further exacerbation(s)

Risk (Increasing Exacerbations)

LAMA/LABA/ICS

ICS/LABA

Persistent symptoms/further exacerbation(s)

Consider rolumilast if FEV₁ <50% predicted and patient has chronic bronchitis

Consider macrolide

Further exacerbation(s)

Preferring treatment pathway =

Recent Key Trials in COPD Management

**FULFIL** – RCT showing triple therapy (LABA/LAMA/ICS) superior to LABA/ICS in terms of improving FEV1 and symptoms, reducing exacerbations.

**TRINITY and TRILOGY** – RCT showing triple therapy (LABA/LAMA/ICS) superior to LAMA (TRINITY) and LABA/ICS (TRILOGY) in terms of improving FEV1 and symptoms, reducing exacerbations.
When would you consider withdrawing an ICS?

ICS "step-down" (de-escalation/substitution if:
  Not ACOS
  No exacerbations or chest infections in last 1-2 years and stable dyspnoea
  Recent pneumonia (CXR confirmed) or other ICS-related complications
  "Low" blood serum eosinophil count (<300-μL⁻¹ or <4%)

"Step-up" (escalation) based on:
  Recent "exacerbation" or chest infection history
  Symptom score (CAT >10) or persistent SOB
  Low or highly variable expiratory flow rates (FEV₁ <50% or <15% or <400 mL)
  "High" blood serum eosinophil count (>300-μL⁻¹ or >4%)

Mild
  Increasing symptoms Persisting SOB or CAT >10

Non-exacerbator
  Persistent symptoms/ SOB and infrequent exacerbator
  LAMA
  LABA
  LABA/ICS

Frequent/recent exacerbator
  Minimally reversible airflow limitation
  LAMA/LABA/ICS
  LABA/ICS

Partially reversible airflow limitation (>400 mL or >15%)

LABA/ICS

Late "irreversible" ACOS phase (>40 years old)
Increasing exacerbations or symptoms

Early "reversible" asthma phase (<40 years old)
Non-pharmacological treatment for COPD

- Vaccinations – Influenza and pneumococcal

- Regular Exercise – optimise physical “fitness” or condition (anti-inflammatory)

- Pulmonary rehabilitation (post hospital discharge or after significant exacerbation) – physical conditioning, confidence and inhaler optimisation

- Diet – Diet high in fruit, vegetables and fibre (Mediterranean Diet)

- Treat underlying **Coronary Artery Disease** risk factors

Global Strategy for the Diagnosis, Management and Prevention of Chronic Obstructive Pulmonary Disease (GOLD) 2014
Cause of death in older heavy smokers according to COPD GOLD grade

- **Lung Cancer Deaths**
- **Cardiovascular Deaths**
- **Respiratory Deaths**
- **Other Cancer Deaths**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Healthy Smokers</th>
<th>GOLD 1</th>
<th>GOLD 2</th>
<th>GOLD 3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung Cancer Deaths</td>
<td></td>
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<tr>
<td>Cardiovascular</td>
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<tr>
<td>Respiratory</td>
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<tr>
<td>Other Cancer</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deaths</td>
<td></td>
<td></td>
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</tbody>
</table>

Graph showing the comparison of cause of death among different COPD GOLD grades.
Cause of death in older heavy smokers according to COPD vs diabetes

- Healthy Nondiabetic
- GOLD 0 Nondiabetic
- GOLD U Nondiabetic
- Unk COPD Nondiabetic
- COPD Nondiabetic
- Healthy Diabetic
- Unhealthy Diabetic
- COPD Diabetic

LC Deaths, CVS Deaths, Resp Deaths, Other cancer Deaths
Changes for Management of Stable COPD:
Summary of new pharmacologic treatment algorithms in 2017 GOLD

<table>
<thead>
<tr>
<th>Group A: SABA and/or SAMA or LAMA*</th>
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<table>
<thead>
<tr>
<th>Group B: Initial therapy should consist of LAMA progressing to LAMA/LABA if patient has persistent symptoms</th>
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</thead>
</table>

<table>
<thead>
<tr>
<th>Group C: Initial therapy should consist of LAMA, progressing to LAMA/LABA (preferred) or ICS/LABA (alternative) if patient has persistent exacerbations or indications for ICS (ACOS or high eosinophils)</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Group D:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial therapy should consist of LAMA/LABA (preferred) or ICS/LABA in ACOS patients or those with high EOS</td>
</tr>
<tr>
<td>If patient develops further exacerbations, LAMA/LABA/ICS is recommended</td>
</tr>
<tr>
<td>If patient develops further exacerbations, roflumilast (not registered in NZ), macrolide or stopping ICS could be considered in certain patients</td>
</tr>
</tbody>
</table>

*Gold states that long acting bronchodilators are preferred over short acting alternatives, with the exception being when patients only have occasional dyspnoea.

Figure 6. Alternate schema to the pharmacologic treatment algorithm for COPD by GOLD group, adapted for the New Zealand setting.41

Confirm COPD (A-D) and ACOS (E) diagnosis with spirometry

**SEVERE**

- Partially reversible airflow limitation (>200 ml or >12%)

**ACOS**

- LA/Ba/ICS
- Minimally reversible airflow limitation
- LAMA/LABA/ICS

**E**

Consider “Step up” (escalation) based on:
- Recent exacerbation or chest infection history
- Symptom Score (CAT>10) or persistent/daily SOB
- Low or highly variable expiratory flow rates (FEV1%<50% or ±15% or ±400 ml)
- Use ICS if “High” blood Eos (≥300/µL or ≥4%)**

**A**

- Frequent/recent exacerbator
- LA/Ba/ICS*

**D**

- Persistent symptoms/SOB and infrequent exacerbator
- LA/Ba/ICS

**B**

- LA/Ba/Ics
- LAMA/LABA

**C**

- SABA/SAMA
- Non-exacerbator

Increasing exacerbations

- (>2/year or hospitalised in last year)

**MILD**

- Increasing Symptoms
- Persisting SOB or CAT>10

- Asthmatic “history” with persistent airflow limitation + aero-pollutant exposure
- ± IgE-mediated (atopic) disease
- ± High blood Eos (≥300/µL)

- “Aero-pollutant” exposure and persistent airflow limitation
- - smoking history (≥10 pack yrs), or
- - occupational/biomas exposures

Consider ICS “step down” (de-escalation/substitution) if:
- Not ACOS
- No exacerbations or chest infections in last 1-2 years and stable dyspnea
- Recent pneumonia (CUR confirmed) or other ICS-related complications
- “Low” blood Eos (<150/µL or <2%)

ACOS = asthma; COPD = chronic obstructive pulmonary disease; CAT = COPD assessment test; CUR = chest radiograph; FEV1 = forced expiratory volume in 1 sec; ICS = inhaled corticosteroids; LABA = long-acting β-agonist; LAMA = long-acting muscarinic antagonist; SABA = short-acting β-agonist; SAMA = short-acting muscarinic antagonist; SOB = shortness of breath