Management of COPD – a paradigm shift.

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COPD Management - confused
COPD Management - Confused

Patient-centred management of stable COPD in primary care

For all patients:
- provide smoking cessation advice
- provide patient education/self management
- assess co-morbidity
- give dietary advice if BMI > 25 kg/m²
- promote exercise
- offer pneumococcal vaccination
- offer annual influenza vaccination
- refer to a dietary specialist if BMI < 20 kg/m²

**SYMPTOMS?**

**BREATHELESSNESS**
- Prescribe short-acting bronchodilators (beta₂ agonist/antimuscarinic) for relief of symptoms

**PERSISTENT SYMPTOMS**
- Offer pharmacotherapy in line with NICE guideline

**PRODUCTIVE COUGH**
- Consider use of mucolytics

**FUNCTIONAL LIMITATION?**

**MRC score ≥2**
- Optimise pharmacotherapy
- See NICE pharmacological algorithm
- Offer pulmonary rehabilitation
- Screen for anxiety/depression

**EXACERBATIONS**

**Oral steroids/antibiotics/hospital admissions**
- Optimise pharmacological therapy
- Discuss action plans including use of standby oral steroids and antibiotics

**HYPOXIA?**

**Oxygen saturation ≤92% at rest in air**
- FEV₁ <30% predicted
- Refer for oxygen assessment

**HOLISTIC CARE**
- Check social support (e.g. carers and benefits)
- Treat co-morbidities
- Consider palliative therapy or secondary care referral for resistant symptoms
- Refer to specialist palliative care teams for end-of-life care
COPD - simplified

But how do you define severity?
Topics

1. What is COPD and why diagnose it
2. Treatment options in COPD – a symptom based approach
3. Treatment options in COPD – when to add the inhaled steroids
4. Treatment options – beyond the airways
1. What is COPD and why diagnose it
“COPD is highly prevalent, underdiagnosed, undertreated and underperceived”

Bart Celli 2008
What is COPD and why diagnose it

- Affects 8% of adult population (1 in 10)
- Affects 20% of adult smokers (1 in 5)
- Affects 30% of adult general medical admissions
- Affects 50% of pneumonia over 65 yrs old

COPD and asthma are very different diseases
Diagnosis, **Assess & Management of COPD**

- Diagnose - assess expiratory flow (spirometry, PEFR)
- Assess symptoms (CAT and MRC score)
- Assess exacerbation risk (PHx of exacerbation, FEV$_1$ %pred)
- Assess COPD co-morbidities (anxiety/depression, muscle wasting/fatigue)
- Assess COPD-related co-morbidities (CHD/CHF, lung cancer, osteoporosis)
- Manage – reduce risk and reduce symptoms
Diagnosis, Assess & Manage COPD

- Diagnose - assess airflow limitation (spirometry, PEFR)
- Assess symptoms (CAT and MRC score)
- Assess risk of exacerbations (PHx of exacerbation)
- Assess COPD comorbidities (anxiety/depression, muscle wasting/fatigue)
- Assess COPD-related comorbidities (CHD/CHF, lung cancer, osteoporosis)
- Manage – reduce risk and reduce symptoms
### Diagnosis, Assess & Manage COPD

<table>
<thead>
<tr>
<th>Diagnose</th>
<th>Assess</th>
<th>Manage</th>
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<td>Manage -</td>
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</table>

**Diagnose**:
- expiratory flow (spirometry, PEFR)

**Assess**:
- symptom score
- Expiratory flow
- Exacerbation rate

**Manage**:
- Manage – reduce risk and reduce symptoms
Spirometry and lung age
Decline of Lung Function: variable susceptibility

- Not Susceptible to Smoke (60%)
- Intermediate Smokers (20%)
- Susceptible Smokers (COPD) (20%)

FEV1 (% of value at age 25 years)

Onset of symptoms
Severe disability
Death

Age (years)
Decline in lung function with COPD severity

Nonsmoker decline is 20-30 mL/yr
Decline in lung function with COPD severity

Diagnosed with screening spirometry of smokers/ex-smokers

Diagnosed with SOB/cough/sputum and wheeze (AECOPD)
Decline of Lung Function: variable susceptibility

↓FEV1: other morbidities apart from COPD
- 5x ↑Lung cancer
-5x ↑ heart attack
- 2-3x ↑ stroke  (Young et al. ERJ 2007)
What is COPD and why diagnose it

- Results from genetic susceptibility and aero-pollutant (smoking) exposure
- Neutrophilic airway inflammation
- Presents with
  - exertional breathlessness and LRTI (cough, sputum, wheeze and SOB)
  - Fatigue and poor exercise tolerance
- Systemic inflammation and co-morbidities
- Precursor illness to 70-80% of all lung cancer
Step 1

- Genetic susceptibility
  Combined effects of susceptibility and protective genetic effects

- Cigarette smoke
  Biomass particles and particulates

- Anti-oxidants

- Anti-proteinases

- Lung inflammation

- Oxidative stress

- Proteinases

- COPD pathology

- Host factors and amplifying mechanisms

- Repair mechanisms

Step 2

Smoking Particles

APC

CXCL8
CXCL10

Naïve CD8

Mature CD8

Perforin & Granzyme

Macrophage

CXCL8

Neutrophil

CXCL8
CXCL10

Naïve CD4

MMP’s
Elastase

Cytokines

Emphysema
Obstructive Bronchiolitis
Hypermucus secretion

Epithelial cells
Step 4


Systemic manifestations and comorbidities of COPD

PJ Barnes and BR Celli
2. A symptom based approach
## Management of COPD – the aims

<table>
<thead>
<tr>
<th>Reduce symptoms</th>
<th>Relieve symptoms</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Improve exercise tolerance</td>
</tr>
<tr>
<td></td>
<td>Improve health status</td>
</tr>
<tr>
<td>Reduce risk</td>
<td>Prevent disease progression</td>
</tr>
<tr>
<td></td>
<td>Prevent and treat exacerbations</td>
</tr>
<tr>
<td></td>
<td>Reduce mortality</td>
</tr>
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</table>

GOLD Strategy Document 2011 (http://www.goldcopd.org/)
Development and progression of COPD – FEV$_1$ vs symptoms

Smoke from tobacco and biomass fuel contains ROS, toxins, and particulate matter

Viral and bacterial infections

Y-axis: FEV$_1$ (% of predicted)

- Stage I
- Stage II
- Stage III
- Stage IV

X-axis: Age (years)

- Asymptomatic
- Progressive dyspnoea
- Systemic disease Comorbidities
- Respiratory failure Death
Treatment options in COPD – a symptom based approach

- Spirometry – document severity of airways obstruction (confirm diagnosis, end organ damage)
- Establish – symptom profile (CAT), tendency to LRTI, AECOPD, hospitalisation for acute exacerbations (direct inhaler treatment).
- Consider COPD a CVS risk factor
- Consider COPD a precursor to lung cancer
A symptom based approach

- Smoking and aero-pollutant (dust) avoidance
- Yearly Flu vaccination, 5 yearly pneumococcal vaccination and regular exercise
- Exertional SOB - prn bronchodilators (SABA)
- Fatigue + poor ET – reg bronchodilators (LABA and LAMA (*FEV1<60% predicted for Tiotropium))
- LRTI/bronchitis/AECOPD – Inhaled corticosteroids with LABA or LAMA (*FEV1<60% predicted)
- 2+ Hospitalisations/yr – triple therapy
SABA prn
then LABA bd
then LABA + ICS bd
then LABA /ICS + LAMA
Plus
• Oral AB/Prednisone
• Pulmonary rehab
• LTOT and surgery/valves
# 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>
A symptom based approach

HEED study

• Lung function alone is a poor predictor of symptoms

• Symptoms of COPD should be assessed regularly in patients with COPD (self administered CAT questionnaire, www.catestonline.co.uk)

• Reduced exercise tolerance was seen in 70% with mild disease (%predFEV1>80%) and 74% with moderate disease (%predFEV1 50-80%).

The CAT questionnaire *(download from - www.catestonline.co.uk)*

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Score/40</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cough</td>
<td>mild 0-10 mod 10-15 severe 15-25 very severe 25-40</td>
</tr>
<tr>
<td>Phlegm</td>
<td></td>
</tr>
<tr>
<td>Tight</td>
<td></td>
</tr>
<tr>
<td>SOB</td>
<td></td>
</tr>
<tr>
<td>Activity</td>
<td></td>
</tr>
<tr>
<td>Confidence</td>
<td></td>
</tr>
<tr>
<td>Sleep</td>
<td></td>
</tr>
<tr>
<td>Energy</td>
<td></td>
</tr>
</tbody>
</table>

**A symptom based approach – CAT 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
A symptom based approach – CAT

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
## CAT Score – patient data

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

**Scoring range 0-40**

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

**Total score**

22
No correlation between QOL and FEV$_1$ severity

- Spearman's rank correlation coefficient: $r = -0.23$
- $P < 0.0001$

- Upper limit of normal

- Breathless walking on level ground

- SGRQ score (CAT)
ECLIPSE showed weak correlation between disease outcome parameters & FEV$_1$

- **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
  - p < 0.001

*Agusti et al. Resp Res 2010*
3. When to start long acting bronchodilators and when to add steroids
COPD Management – adding inhalers

GOLD Therapy at Each Stage of COPD

- **Mild**
  - FEV₁/FVC < 0.70
  - FEV₁ ≥ 80% predicted
  - Active reduction of risk factor(s): influenza vaccination
  - Add: short-acting bronchodilator (when needed)

- **Moderate**
  - FEV₁/FVC < 0.70
  - 50% ≤ FEV₁ < 80% predicted
  - Add regular treatment with one or more long-acting bronchodilators (when needed)
  - Add pulmonary rehabilitation

- **Severe**
  - FEV₁/FVC < 0.70
  - 30% ≤ FEV₁ < 50% predicted
  - Add inhaled glucocorticosteroids if repeated exacerbations

- **Very Severe**
  - FEV₁/FVC < 0.70
  - FEV₁ < 30% predicted or FEV₁ < 50% predicted plus chronic respiratory failure
  - Add long-term oxygen if chronic respiratory failure
  - Consider surgical treatments

A symptom based approach

Eclipse study

• “Frequent exacerbator*” is a specific type of COPD that requires aggressive treatment with combination therapy (preferably fixed dose ICS and LABA)

• “Frequent exacerbators” may be found in those with moderate COPD (22%) and not just severe disease (30-50%).

* 2+ exacerbations per year

The ‘frequent exacerbator phenotype’: Frequency/severity by GOLD Category (1)

<table>
<thead>
<tr>
<th>GOLD II (N=945)</th>
<th>GOLD III (N=900)</th>
<th>GOLD IV (N=293)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% of patients</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospitalised for exacerbation in yr 1</td>
<td>Frequent exacerbations (2 or more)</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>18</td>
<td>33</td>
</tr>
<tr>
<td>22</td>
<td>33</td>
<td>47</td>
</tr>
<tr>
<td>p&lt;0.01</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ECLIPSE 1 year data

Frequent exacerbators represent stable COPD phenotype - independent of severity

- Proportion of subjects experiencing ≥2 exacerbations/year increases year-on-year
- Stable population provides potential to understand the cause(s) of the phenotype

<table>
<thead>
<tr>
<th>Year 1</th>
<th>Year 2</th>
<th>Year 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥2 Exacerb./Yr</td>
<td>409</td>
<td>117</td>
</tr>
<tr>
<td>1 Exacerb./Yr</td>
<td>492</td>
<td>296</td>
</tr>
<tr>
<td>0 Exacerb./Yr</td>
<td>778</td>
<td>79</td>
</tr>
</tbody>
</table>

ECLIPSE 3 year data

New GOLD patient groups

(GOLD Classification of Airflow Limitation)

4 or more

2 or more

Less than 2

2 or more

1 or less

mMRC 0-1

mMRC ≥ 2

CAT < 10

CAT ≥ 10

SYMPTOMS†

(mMRC or CAT score)
New GOLD patient groups

RISK* (GOLD Classification of Airflow Limitation)

- (C) 2 or more
- (D) Less than 2

Symptoms and Risk

RISK* (Exacerbation history)

- 2 or more
- Less than 2

mMRC 0-1
CAT <10

mMRC ≥ 2
CAT ≥10

Symptoms and Risk
New GOLD-defined patient groups

RISK* (GOLD Classification of Airflow Limitation)

- Poor spirometry (FEV%pred≤50%)
- or
- 2+ exacerbations/yr (AB/pred/yr)
  but
  ET= manages hills ok
  Good QOL CAT<10

- Reduced spirometry (FEV%pred>50%)
  or
  0-1 exacerbation/yr (AB/pred/yr)
  but
  ET=manages hills ok
  Good QOL CAT>10

- Poor spirometry (FEV%pred≤50%)
  or
  2+ exacerbations/yr (AB/pred/yr)
  and
  ET≥ SOB up slight hills
  Poor QOL CAT≥10

- Reduced spirometry (FEV%pred>50%)
  or
  0-1 exacerbation/yr (AB/pred/yr)
  and
  ET≥SOB up slight hills
  Poor QOL CAT≥10

RISK* (Exacerbation history)

- Less than 2
- 2 or more

SYMPTOMS† (mMRC or CAT score)

- mMRC 0-1
  CAT <10

- mMRC ≥ 2
  CAT ≥10
New GOLD-defined patient groups

RISK* (GOLD Classification of Airflow Limitation)

1. Reduced spirometry (FEV%pred>50%) or 0-1 exacerbation/yr (AB/pred/yr) but ET=manages hills ok Good QOL CAT>10
2. Poor spirometry (FEV%pred≤50%) or 2+ exacerbations/yr (AB/pred/yr) but ET= manages hills ok Good QOL CAT<10
3. Poor spirometry (FEV%pred≤50%) or 2+ exacerbations/yr (AB/pred/yr) and ET≥ SOB up slight hills Poor QOL CAT≥10

SYMPTOMS† (mMRC or CAT score)

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

(C) “Exacerbator”

(D) Severe (both)

(A) Mild (early)

(B) “Symptomatic”
New GOLD-defined patient groups

**Exacerbator** (wet and wheezy)

- Poor spirometry (FEV%pred≤50%) or 2+ exacerbations/yr (AB/pred/yr)
  - but ET= manages hills ok
  - Good QOL CAT<10

**Symptomatic** (weak and wheezy)

- Reduced spirometry (FEV%pred>50%) or 0-1 exacerbation/yr (AB/pred/yr)
  - but ET=manages hills ok
  - Good QOL CAT<10

**Mild (early)**

- Reduced spirometry (FEV%pred>50%) or 0-1 exacerbation/yr (AB/pred/yr)
  - but ET=manages hills ok
  - Good QOL CAT<10

**Severe (combined)**

- Poor spirometry (FEV%pred≤50%) or 2+ exacerbations/yr (AB/pred/yr)
  - and ET≥ SOB up slight hills
  - Poor QOL CAT≥10

**RISK**

- mMRC 0-1 CAT <10
- mMRC ≥ 2 CAT ≥10

**RISK**

- Less than 2
- 2 or more

**SYMPTOMS† (mMRC or CAT score)**

- SABA or SAMA prn
- ICS/LABA or LAMA
- ICS/LABA and LAMA
<table>
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<tr>
<th>Disease Severity</th>
<th>Phenotypic features</th>
<th>Treatment</th>
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<tr>
<td>A. Mild (early)</td>
<td>Low Sx score - mMRC 0-1, CAT&lt;10 and Fair Spirometry - FEV$_1$ GOLD 1-2, and Low exacerbation rate - 0-1/yr</td>
<td>SABA or SAMA (prn)</td>
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<td>B. Moderate – symptomatic</td>
<td>High Sx score - mMRC 2+, CAT≥10 and Fair Spirometry - FEV$_1$ GOLD 1-2, or Low exacerbation rate - 0-1/yr</td>
<td>LABA or LAMA</td>
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<tr>
<td>“Weak and Wheezy”</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C. Moderate – exacerbator</td>
<td>Low Sx score - mMRC 0-1, CAT&lt;10 and Poor Spirometry - FEV$_1$ GOLD 3-4, or High exacerbation rate - 2+/yr</td>
<td>ICS/LABA or LAMA</td>
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<td></td>
</tr>
<tr>
<td>D. Severe (advanced)</td>
<td>High Sx score - mMRC 2+, CAT≥10 and Poor Spirometry - FEV$_1$ GOLD 3-4, and High exacerbation rate - 2+/yr</td>
<td>ICS/LABA and LAMA</td>
</tr>
<tr>
<td>“Wet, Weak and Wheezy”</td>
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Exacerbation = symptoms of increased cough, SOB ± sputum that required a course of ABs ± prednisone

Spirometry \( \text{FEV}_1/\text{FVC} < 70\% \) with \( \text{FEV}_1 \geq 50\% \) predicted (GOLD1-2) or \( \text{FEV}_1 < 50\% \) predicted (GOLD3-4)
# Summary table of new recommendations

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<th>Treatment</th>
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<td>Low Sx score - mMRC 0-1, CAT&lt;10 and Fair Spirometry - FEV₁ GOLD 1-2, and Low exacerbation rate - 0-1/yr</td>
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<td>High Sx score - mMRC 2+, CAT≥10 and Fair Spirometry - FEV₁ GOLD 1-2, or Low exacerbation rate - 0-1/yr</td>
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**Symptom score**

**Expiratory flow**

**Xacerbation rate**

**Exacerbation** = symptoms of increased cough, SOB ± sputum that required a course of ABs ± prednisone

**Spirometry** $FEV₀/FVC<70\%$, with $FEV₀\geq50\%$ predicted (GOLD1-2) or $FEV₀<50\%$ predicted (GOLD3-4)
Primary analysis: all-cause mortality at 3 years

HR 0.825, p=0.052
17.5% risk reduction

2.6% absolute reduction

SFC 12.6%
Placebo 15.2%

Number alive 1524 1464 1399 1299 1293

Calverley et al. NEJM 2007
Rate of moderate and severe exacerbations over three years

Mean number of exacerbations/year

- Placebo: 1.13
- SALM: 0.97\(^*\)
- FP: 0.93\(^*\)
- SFC: 0.85\(^*\)\(^{†‡}\)

25% reduction

NNT to prevent 1 exacerbation in 1 year = 4

* \(p < 0.001\) vs placebo; \(^{†}p = 0.002\) vs SALM; \(^{‡}p = 0.024\) vs FP

Calverley et al. NEJM 2007
Rate of exacerbations requiring systemic corticosteroids over three years

Mean number of exacerbations/year

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Placebo</th>
<th>SALM</th>
<th>FP</th>
<th>SFC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>0.80</td>
<td>0.64*</td>
<td>0.52*</td>
<td>0.46*†‡</td>
</tr>
<tr>
<td>Reduction</td>
<td>0.80</td>
<td>0.64*</td>
<td>0.52*</td>
<td>0.46*†‡</td>
</tr>
</tbody>
</table>

* p < 0.001 vs placebo; † p < 0.001 vs SALM; ‡ p = 0.017 vs FP

Calverley et al. NEJM 2007
TORCH: Results summary

SFC 50/500, in COPD patients with FEV$_1$ < 60% predicted

- Had a trend towards improved survival vs placebo
- Significantly maintains and improves health status vs placebo and components

- Significantly reduces the rate of exacerbations vs placebo and components
- Significantly improves lung function vs placebo and components

- Is generally well tolerated over 3 years with a lack of significant effect on systemic effects of steroids such as bone and eye disorders in COPD patients

- Led to increase in cases of pneumonia, but with no corresponding increase in mortality with SFC treatment

Calverley et al. NEJM 2007
Consequences of COPD exacerbations

Increased mortality
Accelerated lung function decline
Negative impact on quality of life
Impact on symptoms and lung function
Increased economic costs
Increased Mortality
COPD Phenotypes and treatment

- **Mild disease** (FEV1%pred >50%) - few Sx (SABA/SAMA)

- **Mild disease** (FEV1%pred >50%) - persisting Sx (LABA or LAMA) or 2+ exacerbations/yr (ICS/LABA)

- **Mod-Sev disease** (FEV1%pred ≤50%) - few Sx (ICS/LABA or LAMA)

- **Mod-Sev disease** (FEV1%pred ≤50%) - persisting Sx (ICS/LABA and LAMA) and 2+ exacerbations/yr (ICS/LABA and LAMA)
When to add the steroids

- ICS are needed when patients suffer recurrent exacerbations characterised by productive cough and SOB.
- ICS with LABA are superior to ICS alone and shown to improve lung function, quality of life and survival as do LAMA (TORCH/UPLIFT study).
- Oral steroids for 3-10 days are useful for exacerbations characterised by SOB with productive cough.
4. COPD - Beyond the airways
COPD - Beyond the airways

Systemic inflammation
Cytokines: IL-1β, IL-6, IL-18, TNFα
Acute phase proteins: CRP, SAA

- Genetic factors
- Cigarette smoke
- Biomass fuel
- Lung cancer
- Peripheral lung inflammation
- "spill-over"
- Hypoxia

↓ Physical activity

- Skeletal muscle weakness
- Cachexia

Cardiovascular diseases
- IHD, CCF, hypertension

Metabolic diseases
- Diabetes
- Metabolic syndrome
- Obesity

Bone disease
- Osteoporosis
- Osteopenia

Depression
Beyond the airways

- Muscle fatigue, muscle weakness and cachexia (pulmonary rehab and optimised nutrition)
- Cardiovascular disease, stroke, CHF, pulmonary hypertension (aspirin, statin and β-blockers)
- Insulin resistance, metabolic syndrome, obesity (exercise, calorie restriction, weight loss)
- Osteoporosis (bisphosphonates)
Beyond the airways

- Future treatments will look to reduce [dynamic] hyperinflation measured as IC/TLC ratio rather than to use FEV\textsubscript{1} as a measure of outcome.
- Recent studies suggest that statins reduce hyperinflation by reducing inflammation, improving endothelial function and dilating small airways (clinical trial underway).
- Role of cardiovascular drugs in reducing CVS risk during COPD exacerbations
COPD and lung cancer

- COPD increases the risk of lung cancer by 4-6 fold compared to smokers with normal lung function.
- 70-80% of lung cancer has pre-existing COPD
- 20-30% of deaths in COPD are from lung cancer
COPD overlap with lung cancer
**COPD-Lung Cancer Genetic overlap**

**Loci from GWA studies**

**COPD (Lung Function)**
- 1q23-IL6R
- 5q33- ADAM19/HTR4
- 6p21-AGER
- 6q24- GPR126

**Lung Cancer**
- 1q21- CRP
- 5p15- CRR9/TERT
- 6p21- BAT3
- 6q24- RGS17§

**Overlapping Loci**

Chromosome 4q31 locus in COPD is also associated with lung cancer

**2010**


**2011**

**Abstract:** Recent genome-wide association studies have reported chromosome 4q22.1 is associated with lung function and COPD in a case-control study of current or former smokers with chronic obstructive pulmonary disease (COPD, n = 458), lung cancer (n = 454), or normal lung function and smoking history were comparable between groups. We found (rs7671167) confers a protective effect on smoking-related COPD.


This article was published in the following Dove Press journal:
The Application of Clinical Genetics
2 December 2010
Number of times this article has been viewed
COPD and lung cancer overlap: Underlying biology?

Young and Hopkins, Chest 2011; 140:266 and Respirology 2011
COPD and lung cancer

Current and former smokers recruited for CT screening of lung cancer and CT detected lung cancer (LC)

Spirometry-based COPD

CT-based Emphysema

Normal lungs

70% of all lung cancer from people with COPD

90% of all lung cancer from COPD ± emphysema

Diagnosis of lung cancer delayed

- Sx appear like COPD
- CT delayed (CXR poor for early stage)
Management of COPD - Summary
Management of COPD - summary

**At risk patients**
- Spirometry
- Smoking cessation

**Mild – Intermittent Sx**
- Reg LABA

**Mild – Persistent Sx**
- Reg LABA
- "Infective exacerbators"
- LABA + ICS
- ± LAMA

**Mild – Intermittent Sx**
- Prn SABA

**Significant Disability**
- LTOT
  - Volume reduction/valve surgery
- CVS risk
  - Lung cancer sx

**Significant Co-morbidity**
- ± LAMA

**Mod – Persisting Sx**
- LABA + ICS
- ± LAMA

**CAT questionnaire**
- Vaccinations
  - Prn SABA

**Reg LABA**
## Summary table of new recommendations

<table>
<thead>
<tr>
<th>Disease Severity</th>
<th>Phenotypic features</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A. Mild (early)</strong></td>
<td>Low Sx score - mMRC 0-1, CAT&lt;10 and Fair Spirometry - FEV&lt;sub&gt;1&lt;/sub&gt; GOLD 1-2, and Low exacerbation rate - 0-1/yr</td>
<td>SABA or SAMA (prn)</td>
</tr>
<tr>
<td><strong>B. Moderate – symptomatic</strong></td>
<td>High Sx score - mMRC 2+, CAT≥10 and Fair Spirometry - FEV&lt;sub&gt;1&lt;/sub&gt; GOLD 1-2, or Low exacerbation rate - 0-1/yr</td>
<td>LABA or LAMA</td>
</tr>
<tr>
<td>“Weak and Wheezy”</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>C. Moderate – exacerbator</strong></td>
<td>Low Sx score - mMRC 0-1, CAT&lt;10 and Poor Spirometry - FEV&lt;sub&gt;1&lt;/sub&gt; GOLD 3-4, or High exacerbation rate - 2+/yr</td>
<td>ICS/LABA or LAMA</td>
</tr>
<tr>
<td>“Wet and Wheezy”</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>D. Severe (advanced)</strong></td>
<td>High Sx score - mMRC 2+, CAT≥10 and Poor Spirometry - FEV&lt;sub&gt;1&lt;/sub&gt; GOLD 3-4, and High exacerbation rate - 2+/yr</td>
<td>ICS/LABA and LAMA</td>
</tr>
<tr>
<td>“Wet, Weak and Wheezy”</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Exacerbation** = symptoms of increased cough, SOB ± sputum that required a course of ABs ± prednisone

**Spirometry** FEV<sub>1</sub>/FVC<70% with FEV<sub>1</sub>≥ 50% predicted (GOLD1-2) or FEV<sub>1</sub><50% predicted (GOLD3-4)
### Scoring range 0-40

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>I never cough</td>
<td>0 2 3 4 5</td>
</tr>
<tr>
<td>I have no phlegm (mucus) in my chest at all</td>
<td>0 2 3 4 5</td>
</tr>
<tr>
<td>My chest does not feel tight at all</td>
<td>0 1 3 4 5</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 5</td>
</tr>
<tr>
<td>I am not limited doing any activities at home</td>
<td>0 1 2 3 5</td>
</tr>
<tr>
<td>I am confident leaving my home despite my lung condition</td>
<td>0 1 2 3 5</td>
</tr>
<tr>
<td>I sleep soundly</td>
<td>0 1 2 3 5</td>
</tr>
<tr>
<td>I have lots of energy</td>
<td>0 1 2 3 5</td>
</tr>
</tbody>
</table>

### Total score: 22

---

### Questions?

---

#### FEV1 (% predicted)

- Stage I: 
  - Δ 40 mL/yr
- Stage II: 
  - Δ 47-79 mL/yr
- Stage III: 
  - Δ 56-69 mL/yr
- Stage IV: 
  - Δ < 35 mL/yr

#### GOLD Classification of Airflow Limitation

- **RISK* (Exacerbation history)**
  - Less than 2
  - 2 or more

- **SYMPTOMS† (mMRC or CAT score)**
  - mMRC 0-1
  - mMRC > 2
  - CAT <10
  - CAT >10

#### Symptoms

- I cough all the time
- My chest is completely full of phlegm (mucus)
- My chest feels very tight
- When I walk up a hill or one flight of stairs I am very breathless
- I am very limited doing activities at home
- I am not at all confident leaving my home because of my lung condition
- I don’t sleep soundly because of my lung condition
- I have no energy at all

---

#### Standards for the Diagnosis and Management of Patients with COPD

- **Clinical Presentation**
  - At Risk
  - Symptomatic
  - Exacerbations
  - Respiratory Failure

- **Interventions**
  - Smoking Cessation
  - Disease Management
  - Pulmonary Rehabilitation
  - Other Options

---

### Disease Progression

- FEV1
- Symptoms
5. Management options in the future
Common pathogenic mechanisms and pathways in the development of COPD and lung cancer

Ian A Yang¹, Vandana Relan, Casey M Wright, Morgan R Davidson.

Common pathogenic mechanisms and pathways in the development of COPD and lung cancer

Putative mechanism
Environmental toxins
(Cigarette smoke, air pollutants, carcinogens)

COPD
- Oxidative stress
- Infection
- ↓ Angiogenesis
- Ineffective repair

Epithelial–mesenchymal transition (EMT)
- e.g., - TGFβ
- Wnt, Notch
- Matrix degradation
  - MMPs
- Inflammation
  - NF-κB
  - STAT3
  - IL-6
  - Neutrophil elastase
- Wound repair
- Cell proliferation
- Angiogenesis
  - EGFR
  - HIF
  - VEGF
  - nAChR

Lung cancer
- Self-sustaining growth
- Tissue invasion and metastasis
- Evade immune surveillance
- Limitless replication
- ↑ Angiogenesis

Underlying susceptibility:
Lung cancer risk and clinical utility

Prevention:
Smoking cessation

Early Detection:
Pre-malignant, imaging

Chemoprevention:
NSAID, Iloprost, Statins

Optimised by gene based risk tools
Lung cancer risk and clinical utility

Prevention:
Smoking cessation

Early Detection:
Pre-malignant, imaging

Chemoprevention:
NSAID, Iloprost, Statins

Optimised by gene based risk tools
Lung cancer susceptibility score:

Lung cancer risk score: **Very High Risk** (6 or more)

In addition to smoking, the risk of lung cancer is further increased by:
- genetic factors
- how much you smoked
- age
- COPD.

Respiragene Test* identifies those at greatest risk based on the above factors.

Life-long Smoker – has on average a 1 in 10 (10%) lifetime chance of getting lung cancer.

Non-smoker – has on average a 1 in 200 (0.5%) lifetime chance of getting lung cancer.

*Young RP, et al. PlosOne 2009; April 23.*
Daily cigarette consumption pre- and post genetic testing

<table>
<thead>
<tr>
<th>6 months before testing (n=46 smokers)</th>
<th>6 months after testing (n=46 smokers)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quit</td>
<td>0</td>
</tr>
<tr>
<td>1-5 cigs/day</td>
<td>0</td>
</tr>
<tr>
<td>6-10 cigs/day</td>
<td>14</td>
</tr>
<tr>
<td>11-15 cigs/day</td>
<td>7</td>
</tr>
<tr>
<td>16-20 cigs/day</td>
<td>19</td>
</tr>
<tr>
<td>21-25 cigs/day</td>
<td>1</td>
</tr>
<tr>
<td>26+ cigs/day</td>
<td>5</td>
</tr>
<tr>
<td><strong>Overall</strong></td>
<td><strong>Overall</strong></td>
</tr>
<tr>
<td>78% reduced cigarette consumption</td>
<td>78% reduced cigarette consumption</td>
</tr>
<tr>
<td>13 (28%) Quit smoking</td>
<td>13 (28%) Quit smoking</td>
</tr>
<tr>
<td>2 lost to follow up</td>
<td>2 lost to follow up</td>
</tr>
<tr>
<td>9 (20%) no change</td>
<td>9 (20%) no change</td>
</tr>
<tr>
<td>1 (2%) increased</td>
<td>1 (2%) increased</td>
</tr>
</tbody>
</table>

* diagnosed Prostate cancer after testing

After genetic testing changes in cigs/day:
Overall 78% decreased cigs/day (blue), 13 (28%) Quit smoking, 2 lost to follow up, while 9 (20%) no change (orange) and 1 (2%) increased (red) consumption

* P<0.05
CT screening for lung cancer

NLST trial (November, 2010, NEJM July 2011)
- RCT of >50,000 current and former smokers in the US aged 55-74 yr and with 30+ pack year history
- Compared yearly CT screening with CXR screening over 3 years
- Showed a 20% reduction in lung cancer mortality
- Concerns remain over low pick up rates, costs and harms from radiation and unnecessary investigation of low risk smokers → need to better target high risk smoker
Factors to target (Bechtel et al. Chest 2005; 127: 1140)

- Age >50 yo (90% of LC aged over 50 yr)
- Smoking Exposure (>30 pack years)
- COPD (affects 60-80% of LC cases, 5x ↑risk)
- Family Hx (2-3x ↑risk)
- Genetic factors (?2-10x ↑risk)
- Emphysema on baseline CT (?2x ↑risk)

Non-targeted CT screening

- Low pick up – 1% annual scanning
- Too costly
- Harm (radiation, unnecessary procedures) > benefit

CT Screening for Lung cancer – current approach

Not cost effective CT screening
Lung cancer Screening – Must be Highly Targeted

Factors to target

• Age >50 yo (90% of LC aged over 50 yr)
• Smoking Exposure (>30 pack years)
• COPD (affects 60-80% of LC cases, 5x ↑risk)
• Family Hx (2-3x ↑risk)
• Genetic SNP markers (2-10x ↑risk)
• Emphysema on baseline CT (2x ↑risk)

Respiragene - Lung Cancer Susceptibility score
- utilises top 5 variables above

Non-targeted CT screening

- Low pick up
- Too costly
- Harm > benefit

Maximise specificity over sensitivity – identify more cancers per person screened
Lung Health Clinic (Auckland)

Contact us: Ph 0800 789999 or 09 630 9967 or Fax 09 623 6456 or email: lunghealthclinic@adhb.govt.nz

For assessment of patients with breathlessness or suspected of asthma or COPD (especially those exposed to smoking or aero-pollutants).

For lung function testing, medication review, smoking cessation, inhaler technique, COPD unresponsive to treatment and lung cancer screening.

Refer your patient for a personal consultation with Raewyn Hopkins (BN, MPH) or Associate Professor Robert Young, Consultant Physician (FRACP, PhD)
COPD overlap with lung cancer

Lung Cancer

Emphysema/COPD

Cigarettes