State of the Art: COPD in 2020

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B. Celli Disclaimer

No stocks or ownership in any company.

No Tobacco funds

Advisory boards: GSK, B.I., Astra Zeneca, Novartis, Pulmonx, Chiesi, Menarini.

Member of the Scientific and Executive Committee of GOLD
Agenda

• Describe the COPD landscape in the World
• There are several “natural courses” to develop COPD
• Provide a practical approach to initiate and modify pharmacotherapy in patients with COPD.
• Review the tools available for patients on maximal therapy who remain functionally impaired
• Conclusions
Agenda

• Describe the COPD landscape in the World
COPD

Percent of deaths: 5.36
Annual % change = -1.01
Agenda

• There are several “natural courses” to develop COPD
Course of Lung Function

Determinants of loss

- Current smoking
- Male
- Emphysema
- Low BMI
- Lower CC16 levels
- Higher FEV$_1$

No pharmacological therapy
- Exacerbations
- Pollution
- Poverty

Lange P et al NEJM 2015;372:2
Course of Lung Function

Determinants of gain

TR1: Normal
TR2: Small lungs but no COPD
TR3: Normal initial FEV₁ with rapid decline leading to COPD
TR4: Small lungs leading to COPD

TR1: 71.5%
TR2: 16.9%
TR3: 5.5%
TR4: 6.1%

No COPD
COPD

Lange P et al NEJM 2015;372:2
Agenda

- Provide a practical approach to initiate and modify pharmacotherapy in patients with COPD.
Bronchodilator responsiveness in COPD

n = 5881

FEV$_1$ = 1.1 L

53%

Tashkin D et al. ERJ 2008;31:742
Bronchodilator responsiveness in COPD

FEV$_1$, but not FVC response

- Stage II
- Stage III
- Stage IV

FVC, but not FEV$_1$, but not FVC response

≥15%
≥12% + ≥200 mL

Tashkin D et al ERJ 2008;31:742
TORCH: DB, R, PC, 3 year trial. 6000 patients comparing F, S, SF, P
Outcome: Primary: Mortality  Secondary: FEV1, QoL, Exacerbations

92 ml difference from placebo

25% reduction in exacerbations

St George’s is 3.1 better than placebo and better than baseline

Pneumonia Risk in TORCH

- Older than 55 years
- Lower BMI < 25 Kg/m²
- FEV₁ < 50 % predicted
- Previous exacerbations

Crim C et al ERJ 2009;34:341
UPLIFT: DB, R, PC, 4 year trial. 6000 patients. Tio vs Usual care
Outcome: Primary: FEV1 decline  Secondary: QoL, AE, Mortality

**UPLIFT®**

- 110 ml difference from placebo
- 16% reduction in exacerbations
- St George’s is 3.3 units better than placebo and better than baseline

Tashkin D et al NEJM 2008;359:1543
How to approach?
Diagnosis

Assessment of airflow limitation

<table>
<thead>
<tr>
<th>Grade</th>
<th>FEV&lt;sub&gt;1&lt;/sub&gt; (% 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>
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FEV<sub>1</sub>/FVC<0.7
Diagnosis

Assessment of airflow limitation

Assessment of symptoms/risk of exacerbations

Exacerbation history

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FEV₁/FVC<0.7

- mMRC 0-1
- CAT < 10
- CCQ < 1

- mMRC 2+
- CAT 10+
- CCQ 1+

2 or more hospitalizations

1 or more hospitalization

0 or 1 (no hospitalization)
GOLD 2019: Initial Pharmacological Treatment

INITIAL PHARMACOLOGICAL TREATMENT

- ≥ 2 moderate exacerbations or ≥ 1 leading to hospitalization
- 0 or 1 moderate exacerbation (not leading to hospital admission)

**Group C**

- LAMA

**Group D**

- LAMA or LAMA + LABA* or ICS + LABA†

**Group A**

- A Bronchodilator

**Group B**

- A Long-acting Bronchodilator (LABA or LAMA)

mMRC 0-1 CAT < 10

mMRC ≥ 2 CAT ≥ 10

ICS = inhaled corticosteroid; LABA = long-acting beta₂-adrenergic agonist; LAMA = long-acting muscarinic antagonist.

*Consider if highly symptomatic (e.g., CAT > 20)

†Consider if eosinophils ≥ 300

1. IF RESPONSE TO INITIAL TREATMENT IS APPROPRIATE, MAINTAIN IT.

2. IF NOT:
   ✓ Consider the predominant treatable trait to target (dyspnea or exacerbations)
   - Use exacerbation pathway if both exacerbations and dyspnea need to be targeted
   ✓ Place patient in box corresponding to current treatment and follow indications
   ✓ Assess response, adjust, and review
   ✓ These recommendations do not depend on the ABCD assessment at diagnosis

**DYSPNEA**

**EXACERBATIONS**

*Consider if eosinophils ≥ 300 cells/µL or ≥ 100 cells/µL + ≥ 2 moderate exacerbations or 1 hospitalized exacerbation.

†Consider de-escalation of ICS or switch if pneumonia, inappropriate original indication, or lack of response.
Exacerbations predictors: Post hoc analysis of budesonide in 3 RC COPD trials

Data from 3 RC trials of:
B/F versus F alone who had eosinophils measured

N = 4153 patients

$\text{FEV}_1 = 1 \text{ L} \quad 38\% \text{ pred}$

Outcomes:
Exacerbations
FEV$_1$
QoL

Bafadhel M et al Lancet RM 2018;6:117
LAMA

Symptoms (Dyspnea) and Exacerbations

FEV₁

Make diagnosis and grade risk factors

Initiate Therapy
Supervise inhaler technique
Check adherence

Celli B and Wedzicha J NEJM 2019;381:1257
Symptoms (Dyspnea) and Exacerbations

FEV₁

Make diagnosis and grade risk factors

Emphysema features
Hyperinflation
Eosinophils <100 cells/μL

Asthmatic features
Wheezing, allergies
Eosinophils >100 cells/μL

Initiate Therapy
Supervise inhaler technique and Check adherence

LAMA

Celli B and Wedzicha J NEJM 2019;381:1257
Make diagnosis and grade risk factors

Initiate Therapy
Supervise inhaler technique
and
Check adherence

FEV₁

Symptoms (Dyspnea) and Exacerbations

Emphysema features
Hyperinflation
Eosinophils <100 cells/µL

Symptom persistence

LAMA

LAMA+
LABA

Asthmatic features
Wheezing, allergies
Eosinophils >100 cells/µL

Celli B and Wedzicha J NEJM 2019;381:1257
Make diagnosis and grade risk factors

Initiate Therapy
Supervise inhaler technique and Check adherence

FEV₁

Symptoms (Dyspnea) and Exacerbations

Emphysema features
Hyperinflation
Eosinophils <100 cells/µL

Symptom persistence
LAMA

LAMA+
LABA

Asthmatic features
Wheezing, allergies
Eosinophils >100 cells/µL

LABA+ICS

Check for ICS side effects
If important discontinue and consider alternatives

Celli B and Wedzicha J NEJM 2019;381:1257
Continued lack of control LAMA+ LABA

Symptoms (Dyspnea) and Exacerbations

FEV₁

Emphysema features
Hyperinflation
Eosinophils <100 cells/µL

Asthmatic features
Wheeze, allergies
Eosinophils >100 cells/µL

Frequent and/or severe exacerbations

LABA+ICS

Check for ICS side effects
If important discontinue and consider alternatives

Triple (LAMA+ LABA + ICS)

Make diagnosis and grade risk factors

Initiate Therapy

Supervise inhaler technique and

Check adherence

Celli B and Wedzicha J NEJM 2019;381:1257
LAMA (PDE4i, macrolides, NAC, Xanthines)

Triple (LAMA + LABA + ICS)

Make diagnosis and grade risk factors

Initiate Therapy

Supervise inhaler technique and Check adherence

Check for ICS side effects
If important discontinue and consider alternatives

(PDE4i, macrolides, NAC, Xanthines)

Check for persistent eosinophilia If present, consider biologicals

Celli B and Wedzicha J NEJM 2019;381:1257
Agenda

• Review the tools available for patients on maximal therapy who remain functionally impaired
Along with 31 RCT’s included in the 2006 Cochrane Review, the authors included 34 additional RCT’s with a grand total of 3,822 participants.

“We found statistically and clinically significant improvements in important domains of health related quality of life, including dyspnea, fatigue, emotional function and mastery as well as in the 6 MWD, a test of functional capacity.”
Hyperinflation in a 63 year old man with mMRC dyspnea of 3

FEV$_1$ = 32 %
FRC = 192 %
DLCO = 49 %
Endobronchial Valves (EBV)

- Zephyr (Pulmonx)
  - silicone based mounted in a nitinol stent one way valve
- Spiration (Olympus)
  - 6 Nitinol struts and polyurethane umbrella shape unidirectional valve
Endobronchial Valves for Emphysema without Interlobar Collateral Ventilation

Karin Klooster, Nick H.T. ten Hacken, M.D., Ph.D., Jorine E. Hartman, Ph.D., Huib A.M. Kerstjens, M.D., Ph.D., Eva M. van Rikxoort, Ph.D., and Dirk-Jan Slebos, M.D., Ph.D.

A Primary Outcomes in the Intention-to-Treat Population

- **FEV₁**
  - Change from Baseline to 6 Mo (m)
  - EBV (N=34) vs Control (N=34)
  - P=0.002

- **FVC**
  - Change from Baseline to 6 Mo (m)
  - EBV (N=34) vs Control (N=34)
  - P=0.005

- **6MWD**
  - Change from Baseline to 6 Mo (m)
  - EBV (N=34) vs Control (N=34)
  - P=0.001

- **SGRQ Score**
  - Change from Baseline to 6 Mo (points)
  - EBV (N=24) vs Control (N=33)
  - P<0.001
Conclusions

• COPD is an important health problem worldwide
• Although cigarettes remain the most important cause, this is not so for the majority of countries in the world
• Well applied pharmacotherapy works
• In patients with persistent symptoms consider rehabilitation
• Check for emphysema and hyperinflation for potential LVR
• A nihilistic approach is not justified!
“If it were not for the great variability among individuals, medicine might as well be a science and not an art”

William Osler