Bartolome R. Celli, MD graduated from Universidad Central de Venezuela, completed his training in Internal Medicine, and was Chief Medical Resident, at the Boston City Hospital. He then trained in Pulmonary and Critical Care Medicine at the Boston University School of Medicine. Currently, he is Professor of Medicine at Tufts and Harvard Medical School. Together with his wife, Doris, they have raised 4 children, all of them now married with a total of 10 grandchildren ranging in age from 1 to 22 years. The greatest achievement of his life is to have helped raise and educate citizens capable of contributing to make the world a little better. Bart and Doris have reside in Wellesley, Massachusetts for 35 years, where they have been active in their parish and community life.

Dr. Celli has published over 320 peer reviewed scientific papers, 375 abstracts and edited several books. His work includes studies on respiratory muscles and control of breathing that defined the interaction between upper extremity unsupported exercise and the respiratory muscles of the shoulder girdle. These studies prompted interest and subsequent studies that formalized the use of upper extremity exercise in the rehabilitation of patients with COPD. With his team, they have studied the response to systemic exercise in patients with COPD and the effect of intra-thoracic pressures on heart function. He directed two trials of non-invasive ventilation (negative pressure and positive pressure) on clinically meaningful COPD outcomes. He completed a series of studies to determine the relevance of static hyperinflation not just on lung mechanics (well-known for many years) but as an independent predictor of survival. The concept of the inspiratory fraction provided by the IC/TLC was first expressed from work in his group. The group he works with explored tissue micro-arrays for gene expression in emphysema versus mild COPD, serum proteomics and metabolomics in relation to clinically relevant outcomes in patients with COPD and smokers at risk for COPD. Further, joined by excellent trainees and knowing that there is a lack of long observational cohorts of patients with COPD, they organized the BODE cohort of over 2000 patients, describing a significant body of novel clinical findings that have helped develop the field of COPD. The findings include the description of the BODE index as a predictor of mortality raising the concept of multidimensional compromise in COPD. In addition, the
heterogeneity of COPD progression, the value of the 6 Minute walk distance and recently the relationship between co-morbidites such as lung cancer and COPD.

Dr. Celli has been the Chairman of the Committee that established the American Thoracic Society and European Respiratory Society guidelines for the diagnosis and treatment of COPD. In addition, he is in the Scientific Committee of the Global Obstructive Lung Disease initiative and currently serves in the Board of Directors of GOLD. He has also been Chairman of the Clinical Assembly of the ATS and President of the Massachusetts Thoracic Society and New England College of Chest Physicians. In the professional arena, although caring for patients provides him with unique pleasure, he believes his greatest achievement is to have personally helped mentor many young careers in Medicine. Ten Professors of Medicine, one Dean and two Vice-Deans of medical schools in the United States, Venezuela and Colombia are among the 65 individuals in whom he helped instill a love for the profession, a desire to generate new knowledge, and respect for our fellow humans and for the world at large. His trainees are located in the United States, Europe, the Middle East, Japan and Latin America.

**OBJECTIVES:**

1. Learn about the extent of prevalence of COPD in the population at large.
2. Recognize the problem of underdiagnosis in COPD.
3. Introduce the concept of the multiple domains of COPD.
4. Provide evidence of the multiple forms of therapy available to treat the disease.
COPD pharmacotherapy: Reasons for optimism

Bartolome R. Celli, M.D.
Professor of Medicine
Harvard Medical School

B. Celli Disclaimer

No stocks or ownership in any company.
No Tobacco funds
Grants: Astra Zeneca
Advisory boards: GSK, B.I., Astra Zeneca, Novartis, Pulmonx, Chiesi, Menarini.
Objective

- A big problem that progresses over a long period of time
- Patients respond to therapy
- Bronchodilators
- Anti-inflammatories
- New agents
- A logical approach

Objective

- A big problem
Prevalence of COPD

www.GBD
Accessed 8/2018
Underdiagnosis in COPD

![Graph showing underdiagnosis in COPD](image)

Soriano et al. Lancet 2009;721

Smoking: still a problem

![Image showing smoking prevalence by region](image)
E cigarettes

Vaping

Sales in USA in 2013 $1 billion
Objective

- Progresses over a long period of time

Course of Lung Function

Determinants of gain

Lange P et al NEJM 2015;372:2
Objective

- Patients respond to therapy

Bronchodilator response Distribution in UPLIFT

- $n = 5881$
- $\text{FEV}_1 = 1.1 \text{ L}$

Tashkin ERJ 2008
**UPLIFT: FEV₁ versus FVC response**

**FEV₁, but not FVC response**
- Stage II
- Stage III
- Stage IV

**FVC, but not FEV₁ response**
- Stage II
- Stage III
- Stage IV

Tashkin et al ERJ 2008

**Benefits of maximal bronchodilation on clinical outcomes**

Correlation between change in FEV₁ and outcomes:
- TDI vs ΔFEV₁ (mL) P<0.0001, r²=8.2%
- ΔSGRQ vs ΔFEV₁ (mL) P<0.0001, r²=10%
- Number of exacerbations vs ΔFEV₁ (mL) P<0.002, r²=5.6%

Correlation analysis of pooled data from three indacaterol studies (N=3313)

TORCH: DB, R, PC, 3 year trial. 6000 patients comparing F, S, SF, P
Outcome: Primary: Mortality   Secondary: FEV1, QoL, Exacerbations

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

92 ml difference from placebo

25% reduction in exacerbations


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
Case Presentation

• A 73 year old man smoker of 31 pack years has been admitted to the hospital for two episodes of pneumonia over the past one year.
• He has purulent sputum production. Currently on tiotropium, salmeterol and ICS. Received iv corticosteroids for exacerbation of COPD in the past.
• PE shows tachycardia, tachypnea, fever of 39 degrees centigrade. BMI of 17 kg/m2. O2 saturation of 82% on room air and decreased breath sounds.
• Chest X-ray confirms dense infiltrates in RLL
Case Presentation

A. Begin in-hospital rehabilitation
B. D/C inhaled corticosteroids and start supplemental oxygen
C. Start oxygen and consider the patient for non-invasive-ventilation
D. CT scan to evaluate for other reasons for dyspnea
E. Transfer to ICU and monitor for intubation

Question 1 (Celli) - Case Presentation Question 2

A. Begin in-hospital rehabilitation
B. D/C inhaled corticosteroids and start supplemental oxygen
C. Start oxygen and consider the patient for non-invasive-ventilation
D. CT scan to evaluate for other reasons for dyspnea
E. Transfer to ICU and monitor for intubation
LAMA

Glycopirronium  Umeclidinium  Aclidinium  Reveferacin

Combinations?

Ultra LABA + LAMA

LABA + ICS

LABA + LAMA + ICS
Are 2 BD better than 1?

Systematic Review of LAMA/LABA

Meta-analysis of 14 studies and 1 abstract.
Monocomponents = 12,840  Combinations = 10,328

Calzetta L et al CHEST 2016;149:1188
Systematic Review of LAMA/LABA

Meta-analysis of 14 studies and 1 abstract. 
Monocomponents = 12,840  Combinations = 10,328

![Graph showing comparison between monocomponents and combinations](Caizetta L et al CHEST 2016;149:1188)

Are 3 (LABA + LAMA +ICS) better than 2?
Tiotropium + (Placebo, Salmeterol, or S/F) in COPD

n = 449
1 year
FEV₁ = 1.02 L
Primary Outcome
Exacerbations

Aaron S et al Ann Intern Med 2007;146:545

Extraline inhaled triple therapy versus dual bronchodilator therapy in chronic obstructive pulmonary disease (TRIBUTE)

Treatment with the single inhaler combination of BDP/FF/G bid is compared to inhaled IND/G in the prevention of exacerbations in severe and very severe COPD patients with a history of at least one or more moderate and severe exacerbation the year prior to enrollment

**Extrafine inhaled triple therapy versus dual bronchodilator therapy in chronic obstructive pulmonary disease (TRIBUTE)**

Treatment with the single inhaler combination of BDP/FF/G bid is compared to inhaled IND/G in the prevention of exacerbations in severe and very severe COPD patients with a history of at least one or more moderate and severe exacerbation the year prior to enrollment.

No increased pneumonia risk

4% each arm

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**Reduction in fatal events with extrafine inhaled corticosteroid (ICS)-containing medications: results of stratified safety pooled analysis of the TRILOGY, TRINITY and TRIBUTE studies.**

All cause mortality pooling results from the 3 studies

<table>
<thead>
<tr>
<th>N of patients with events (%)</th>
<th>BDP/FF/G (N=3745)</th>
<th>TIO, IND/GLY (N=1844)</th>
<th>HR (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory</td>
<td>19 (0.5%)</td>
<td>9 (0.5%)</td>
<td>1.01</td>
<td>0.45-2.2</td>
</tr>
<tr>
<td>Non-respiratory</td>
<td>56 (1.5%)</td>
<td>41 (2.2%)</td>
<td>0.65</td>
<td>0.43-0.97</td>
</tr>
</tbody>
</table>

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Fabbri L et al ERS 2018 A12381.
Treatment with FF/UME/VI compared with FF/VI and UME/VI in Patients with COPD

**IMPACT trial**

Lipson D et al NEJM 2018; 378(18):1671-1680

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**Table 2. trough FEV₁ and St. George’s Respiratory Questionnaire (SGRQ) Total Score (Intention-to-Treat Population)**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Triple Therapy (N=4112)</th>
<th>Placebo Ferumoxides-Vilanterol (N=4140)</th>
<th>Umeclididine-Vilanterol (N=4170)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trough FEV₁</td>
<td>3386</td>
<td>3380</td>
<td>3380</td>
</tr>
<tr>
<td>Mean change from baseline (95% CI) — ml</td>
<td>127 (121, 134)</td>
<td>117 (112, 123)</td>
<td>122 (117, 127)</td>
</tr>
<tr>
<td>Mean change from baseline (95% CI) — yr</td>
<td>34 (30, 38)</td>
<td>31 (27, 35)</td>
<td>34 (30, 38)</td>
</tr>
<tr>
<td>Difference between triple therapy and dual-therapy comparator (95% CI) — ml</td>
<td>107 (99, 115)</td>
<td>98 (90, 106)</td>
<td>98 (90, 106)</td>
</tr>
<tr>
<td>Difference between triple therapy and dual-therapy comparator (95% CI) — yr</td>
<td>54 (46, 62)</td>
<td>46 (38, 54)</td>
<td>46 (38, 54)</td>
</tr>
<tr>
<td>No. of patients evaluated</td>
<td>3318</td>
<td>3320</td>
<td>3470</td>
</tr>
<tr>
<td>Mean change from baseline (95% CI) — ml</td>
<td>45.4 (43.5 to 47.4)</td>
<td>46.8 (45.1 to 47.4)</td>
<td>46.8 (45.1 to 47.4)</td>
</tr>
<tr>
<td>Mean change from baseline (95% CI) — yr</td>
<td>-3.3 (-5.0 to -1.6)</td>
<td>-3.7 (-4.3 to -3.2)</td>
<td>-3.7 (-4.3 to -3.2)</td>
</tr>
<tr>
<td>Difference between triple therapy and dual-therapy comparator (95% CI) — ml</td>
<td>-1.3 (-2.8 to -0.1)</td>
<td>-2.6 (-3.7 to -1.6)</td>
<td>-2.6 (-3.7 to -1.6)</td>
</tr>
<tr>
<td>Response according to SGRQ total score at wk 52</td>
<td>1721 (42)</td>
<td>1990 (34)</td>
<td>696 (34)</td>
</tr>
<tr>
<td>Odds ratio for triple therapy vs. dual-therapy comparator (95% CI)</td>
<td>1.41 (1.29 to 1.55)</td>
<td>1.41 (1.28 to 1.57)</td>
<td>1.41 (1.28 to 1.57)</td>
</tr>
</tbody>
</table>

*The means presented are least-squares means.

**Note:**
- Total scores on the SGRQ range from 0 to 100, with lower scores indicating better health-related quality of life.
- A response was defined as a decrease in the SGRQ total score of at least 4 units, as compared with the baseline value.
Treatment with FF/UME/VI compared with FF/VI and UME/VI in Patients with COPD
IMPACT trial

Treatment with the single inhaler combination of FF/UME/VI q.d. was compared with FF/VI and UME/VI q.d in 10,355 COPD patients over 1 year

All cause mortality in the three treatments

<table>
<thead>
<tr>
<th></th>
<th>FF/UME/VI (4151)</th>
<th>FF/VI (4170)</th>
<th>UME/VI (2070)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (%)</td>
<td>50 (1)</td>
<td>49 (1)</td>
<td>39 (2)</td>
</tr>
<tr>
<td>HR and 95% CI</td>
<td>0.58 (0.38-0.88)</td>
<td>0.61 (0.4-0.93)</td>
<td>Ref</td>
</tr>
<tr>
<td>Difference</td>
<td>- 42%</td>
<td>- 39%</td>
<td></td>
</tr>
<tr>
<td>p value</td>
<td>0.01</td>
<td>0.02</td>
<td></td>
</tr>
</tbody>
</table>

Increased pneumonia risk on ICS groups 4, 4 and 3% respectively

Lipson D et al. NEJM 2018; 378(18):1671-1680

Other anti-inflammatories?
Azithromycin for prevention of exacerbations of COPD

More hearing problems (28 vs 24%)  \( p = 0.04 \)

Patients on Azithromycin were more likely to be colonized by resistant organisms but no clinical consequences were observed.

Systematic Review and Meta-analysis: Roflumilast

Yuan L et al IJCOPD 2016;11: 1477
How to approach?

Diagnosis

Assessment of airflow limitation

<table>
<thead>
<tr>
<th>Grade</th>
<th>FEV₁ (% pred.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>≥80</td>
</tr>
<tr>
<td>2</td>
<td>50-79</td>
</tr>
<tr>
<td>3</td>
<td>30-49</td>
</tr>
<tr>
<td>4</td>
<td>&lt;30</td>
</tr>
</tbody>
</table>

FEV₁/FVC<0.7
Evolution in GOLD Reports: Initial pharmacological therapy

This schema removed FEV$_1$ from the left vertical axis in GOLD 2015

- \( \geq 2 \) moderate exacerbations or \( \geq 1 \) leading to hospitalization
- 0 or 1 moderate exacerbation (not leading to hospitalization)

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

CAT=COPD Assessment Test; mMRC=modified Medical Research Council.

**GOLD 2019: Initial Pharmacological Treatment**

### INITIAL PHARMACOLOGICAL TREATMENT

<table>
<thead>
<tr>
<th>Group</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group C</td>
<td>LAMA</td>
</tr>
<tr>
<td>Group D</td>
<td>LAMA or LAMA + LABA* or ICS + LABA†</td>
</tr>
<tr>
<td>Group A</td>
<td>A Bronchodilator</td>
</tr>
<tr>
<td>Group B</td>
<td>A Long-acting Bronchodilator (LABA or LAMA)</td>
</tr>
</tbody>
</table>

- **≥ 2 moderate exacerbations or ≥ 1 leading to hospitalization**
- **0 or 1 moderate exacerbation (not leading to hospital admission)**
- 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 (eg, CAT > 20)

†Consider if eosinophils ≥ 300

**GOLD 2019: FOLLOW-UP PHARMACOLOGICAL TREATMENT**

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.

Symptoms (Dyspnea) and Exacerbations

Make diagnosis and grade risk factors

$FEV_1$

Emphysema features Hyperinflation Eosinophils <100 cells/µL

Asthmatic features Wheezing, allergies Eosinophils >100 cells/µL

Initiate Therapy Supervise inhaler technique and Check adherence

Single bronchodilator LAMA or LABA

Celli B CHEST 2018; Chest. 2018 Jul 17. pii: S0012-3692(18)31061-4 (e-published)
Make diagnosis and grade risk factors

FEV₁

Symptoms (Dyspnea) and Exacerbations

Emphysema features
Hyperinflation
Eosinophils <100 cells/µL

Asthmatic features
Wheezing, allergies
Eosinophils >100 cells/µL

Single bronchodilator
LAMA or LABA

2 bronchodilators
LAMA+LABA

LABA+ICS

Symptom persistence

Frequent and/or severe exacerbations

Check for ICS side effects

If important discontinue and consider alternatives

2 bronchodilators
LAMA+LABA

Triple (LAMA+LABA+ICS)

Celli B. CHEST 2018; Chest. 2018 Jul 17. pii: S0012-3692(18)31061-4 (e-published)
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”"
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.
Question

Which of the following is true about patients with very severe COPD (FEV$_1$ < 35% of predicted)

A. They show some FEV$_1$ response but more FVC response than patients with milder obstruction.
B. Lung transplant is not an option.
C. Pulmonary rehabilitation is not effective because it induces peripheral muscle fatigue.
D. Oxygen therapy is always necessary and useful
E. Usually have poor response to triple therapy

Question 2 (Celli) - Which of the following is true about patients with very severe COPD (FEV$_1$ < 35% of predicted)

A. They show some FEV$_1$ response but more FVC response than patients with milder obstruction.

B. Lung transplant is not an option.

C. Pulmonary rehabilitation is not effective because it induces peripheral muscle fatigue.

D. Oxygen therapy is always necessary and useful

E. Usually have poor response to triple therapy
Conclusions

- We need to promote healthy lifestyles and battle against smoking and pollution
- There is a need to improve diagnosis of COPD
- Pharmacotherapy is effective if well used
- Rehabilitation is a “must consider”
- Onwards, the future is ours to build
Thank You................................Make sure you do the most important thing!!!!!

[Image: NAPA VALLEY sign with welcoming message]