WALTER O’DONOHUE LECTURE

CHANGING THE NATURAL COURSE OF COPD

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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-morbidities 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.
The Changing Natural History of COPD
Role of Co-morbidities

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

Agenda

• An old disease (Revive the classics)
• The Dogma and the Doubts
• Reality and the Optimism
• Aging, comorbidities and their impact on COPD progression
• Conclusions
**Agenda**

- An old disease (Revive the classics)

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**COPD**

Laennec R. A treatise on diseases of the lungs. C Underwood. London 1821

“The disease can begin in infancy, and continue for many years. More often cough with mucous catarrh, worsens in winter and in the mornings. Often accompanied by difficult respiration, might end fatally by “suffocative catarrh” Once present, dyspnea is constant, worsened by anxiety and exercise and above all by supervision of acute catarrh”
Agenda

• The Dogma and the Doubts

• The Dogma!
COPD: Fletcher and Peto’s model. Figure 1

BMJ 1977;1:1645

749 men followed for 8 years
Chasing the Holy Grail
AC: 68 year old housewife

- Dyspnea for 14 years.
- Current smoker of 2.5 ppd for 52 years (136 pk/yr)
- History of: Graves Disease (Hypothyroid), CAD, Hypertension, Hyperlipidemia, Diabetes, Depression, GERD, Osteoporosis, OSA (On CPAP), Obesity and Fibromyalgia
- On: LAMA, ICS/LABA, Roflumilast, Monterleukast, Prednisone, SABA. Uses nebulizer prn.
- BMI: 43  mMRC: 4  6MWD: 90 meters.  FEV$_1$: 0.8 L (22%)  BODE: 9

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Mean FEV$_1$ Values by Age, for Healthy Never-smokers (NS), Versus Continuous Smokers (CS)


COPD GOLD stages in Patients Under 50 Years of Age (UPLIFT)

Rate of FEV$_1$ decline in 3 observational studies of patients with COPD

- **Casanova C et al AJRCCM 2011;184:315**
  - N = 751
  - F/U = 10 YEARS
  - Rapid decliners: 18%
  - Normal decliners: 82%

  - N = 2163
  - F/U = 3 YEARS
  - Rapid decliners: 7%
  - Normal decliners: 36%
  - Improvers: 57%

- **Nishimura M et al AJRCCM 2012;185:44**
  - N = 260
  - F/U 5 YEARS
  - Rapid decliners: 25%
  - Normal decliners: 25%
  - Improvers: 50%

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• *The Evidence*
CCHS: Baseline FEV$_1$ and development of GOLD II COPD

![Graph showing FEV$_1$ vs. Age (years)]

Lange P et al NEJM 2015;372:2

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

Agenda

• The Reality
Rate of FEV$_1$ decline in NS in 3 studies: 1999 to 2012

Rate of FEV$_1$ decline in selected randomized trials: 1999 to 2016
Rate of FEV$_1$ decline in selected randomized trials: 1999 to 2016

-23 ml/yr

Δ Active versus placebo 9 ml/year

COPD: Change in GOLD Stages over 8 years of follow-up  BODE cohort  N = 318

No change 62%

Improved 9%

Progressed 29%

De Torres JP et al PLOSONE 2016 Apr 21;11(4):e0151856. doi
COPD: Change in GOLD Stages over 8 years of follow-up  BODE cohort  N = 318

De Torres JP et al PLOS ONE 2016 Apr 21;11(4):e0151856. doi

Mortality in COPD pharmacological trials longer than 1 year

TORCH  UPLIFT  TIOSPIR  SUMMIT
Mortality in COPD pharmacological trials longer than 1 year

Annual % change 1990-2013
Death 100K persons

Communicable
Injuries

Non Communicable

IHD, Stroke, COPD, Diabetes, CKD, Alzheimer, IHD, Stroke, COPD, Diabetes, CKD, Alzheimer, IHD, Stroke, COPD, Diabetes, CKD, Alzheimer, IHD, Stroke, COPD, Diabetes, CKD, Alzheimer, IHD, Stroke, COPD, Diabetes, CKD, Alzheimer, IHD, Stroke, COPD, Diabetes, CKD, Alzheimer
**COPD**
- Percent of deaths: 5.36
- Annual % change: -1.01

**Asthma**
- Percent of deaths: 0.77
- Annual % change: -1.77

**ILD**
- Percent of deaths: 0.23
- Annual % change: +2.42

**Lung Cancer**
- Percent of deaths: 3.12
- Annual % change: +0.63

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**World Smoking Prevalence in 2012**

- Kiribati
- Sudan

**World Smoking Prevalence over time**

- 1980: 0%
- 1990: 50%
- 2000: 50%
- 2010: 50%
Question

Which of the following about COPD is false?
A Its importance as a major health burden is increasing
B Improvement can only be achieved with smoking cessation
C The natural course of the disease can be modified
D In the USA it is the 3rd cause of death
E It may be associated with important systemic manifestations
Agenda

- Aging, comorbidities and their impact on COPD progression

The Ageing Population

1970

Co-morbidities: Two disorders or illnesses occurring in the same person, simultaneously or sequentially

Multimorbidity: The existence of multiple long term conditions in one individual

Co-morbidities and COPD

Random?  Not random?
Prevalence, and outcomes of DM, HTN and CVD in COPD

Mortality in 22,296 subjects in ARIC and CVHS who had GOLD obstruction

TORCH: Causes of death as adjudicated by the Endpoint Committee

Mannino D et al ERJ 2008; 32: 962

Wise et al PATS 2006
Definitions and Basic concepts

• The biology of humans is complex
Definitions and Basic concepts

Systems Biology is the computational and mathematical modeling of complex biological systems.

Agenda

- Scale Free and Random Networks and Network building
What are network graphs?

- Networks are a way of mapping the interconnectivity of objects.
- Elements of a Network graph are **Nodes** and **Edges**.
- Size of nodes represent the size, weight, prevalence.
- Thickness of the edge represent correlation strength (rho) and polarity.

C1

C2

C3

What are network graphs?

- The number of edges in a Node represent its connectivity called “Degree”.
- Nodes and edges position are determined by a computational procedure of attraction and repulsion based on the prevalence, the number and the polarity of its edges.
- Clusters are unfolded as results of their connectivity and position.

Agenda

• Extending the concept to the patient with COPD (clinical view)

Your Patient

78 comorbidities

Divo et al AJRCCM 2012;186:155
Comorbidities prevalence and mortality risk in COPD: The Co-morbidome

Divo et al AJRCCM 2012;186:155
COPD (n = 1969) Comorbidities Network compared to Non-COPD (n = 359)

Cluster 1

Divo M et al ERJ 2015;46:640

Divo M et al ERJ 2015;46:640
Cluster 3

- Leukemia
- Breast CA
- Pancreatic
- Gastro-duodenal ulcers
- Esophageal CA
- Liver CA
- Brain CA
- Schizophrenia Disorders
- Bipolar Disorders
- Depression
- Substance Abuse
- Celiac disease
- Brain metastasis
- Liver cirrhosis
- Hepatitis
- Lung CA
- Age < 55

Divo M et al ERJ 2015;46:640

Temporal disease trajectories condensed from population-wide registry data covering 6.2 million patients

All in-patient admissions, ER and outpatient visits or a total of 101 million ICD-9 codes

Over 14.9 years

Authors were able to define 1,171 trajectories

Amongst them COPD

Jensen A.B. et al Nature Communications 2014 15:4022 DOI: 10.1038/ncomms5022
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Jensen A.B. et al Nature Communications 2014

n = 27,617 patients with diagnosis of COPD

n = 27,617 patients with no COPD

Epichron and BODE groups

Divo et al PLOSone 2018
Comorbidities by age and mortality. Province of Aragon

n = 27,617 patients with diagnosis of COPD
n = 27,617 patients with no COPD

Epichron and BODE groups
Divo et al. PLOSone

Solid dots represent COPD patients and hollow dots represent non-COPD
Epichron and BODE groups
Divo et al. PLOSone
Conclusions

• The natural course of COPD has changed
• COPD is associated with certain co-morbidities above and beyond that of chance alone
• The presence of CO-morbidities influence the “natural” course of COPD
• The future is ours to explore

Thank You  Walter for leading the way