UPDATES IN COPD

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ACP Meeting 12 September 2019
No Financial Disclosures

Specific Drugs May Be Mentioned
OUTLINE

- Refresher
- COPD Definition
- Epidemiology
- Pathogenesis
- Dyspnea
- Systemic manifestations
- Therapeutic considerations
- AECOPD
- Phenotype analysis
- Comprehensive COPD Clinic
- Novel Directions
REFRESHER
Chronic Obstructive Pulmonary Disease (COPD) is a common, preventable and treatable disease that is characterized by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases.
Spirometry

Obstruction:
- FEV1/FVC < 0.7
- OR
- FEV1/FVC < LLN*

*LLN = lower limit of normal = 2 standard deviations below the mean ratio for an age-, sex- & height-matched control subject
**SPIROMETRY**

### Effort-dependent
- **Expiration**
- **Obstruction**

### Effort-independent
- **Gas escapes the lungs at low flows**

### Abrupt decrease in flow: loss of elastic recoil due to damaged connective tissue in the lungs
LOW DLCO ONLY
Post-bronchodilator $\text{FEV}_1$

### Classification of Airflow Limitation Severity in COPD (Based on Post-Bronchodilator $\text{FEV}_1$)

<table>
<thead>
<tr>
<th>Gold</th>
<th>Severity</th>
<th>FEV$_1$ Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Mild</td>
<td>$\geq 80%$ predicted</td>
</tr>
<tr>
<td>2</td>
<td>Moderate</td>
<td>$50% \leq \text{FEV}_1 &lt; 80%$ predicted</td>
</tr>
<tr>
<td>3</td>
<td>Severe</td>
<td>$30% \leq \text{FEV}_1 &lt; 50%$ predicted</td>
</tr>
<tr>
<td>4</td>
<td>Very Severe</td>
<td>$\text{FEV}_1 &lt; 30%$ predicted</td>
</tr>
</tbody>
</table>

**In patients with $\text{FEV}_1/\text{FVC} < 0.70$:**

- Simple
- Correlates with some clinical outcomes: mortality
- BUT, it does not address a lot of other stuff important in COPD

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Epidemiology
>250 known compounds of combustion w/ adverse health effects

Each puff has $\sim10^{15}$ radical molecules

Tobacco smoke is the leading cause of COPD in the US


CDC. MMWR 2005;54:625-28
EPI: SEX-DIFFERENCES IN COPD

Pertaining to COPD, women:

- Suffer more adverse consequences- breathlessness, dysfunction, depression, etc.\(^1\)
- Develop COPD earlier than men\(^2\)
- Have increased loss of resp function for the same smoke exposure as men\(^3-4\)
- Manifest more symptoms over their lifetime\(^5\)

\(^1\)Respir Res 2005;6:45
\(^3\)Am Rev Respir Dis 1991;143:1224–30
\(^4\)Respir Med 2006;100:1110-16
\(^5\)Int J COPD 2018. PMID: 30319250
Figure 2: Graphic representation of the risk factors for chronic obstructive pulmonary disease during the different stages of life. Risk factors are shown for in utero and perinatal life (upper left corner), early childhood (lower left corner), and adulthood (lower right corner). General risk factors are also shown (upper right corner). COPD = chronic obstructive pulmonary disease.
### Global Burden of Disease: Worldwide Mortality 1990 vs 2010

<table>
<thead>
<tr>
<th>Rank (95% UI)</th>
<th>Disorder</th>
<th>1990 Rank</th>
<th>2010 Rank</th>
<th>Mean rank (95% UI)</th>
<th>% change (95% UI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-2</td>
<td>Ischaemic heart disease</td>
<td>1-2</td>
<td>1-2</td>
<td>(1 to 1)</td>
<td>(1 to 1)</td>
</tr>
<tr>
<td>2-1</td>
<td>Stroke</td>
<td>2-1</td>
<td>2-1</td>
<td>(1 to 2)</td>
<td>(2 to 3)</td>
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<tr>
<td>3-4</td>
<td>Lower respiratory infections</td>
<td>3-4</td>
<td>3-4</td>
<td>(3 to 4)</td>
<td>(3 to 4)</td>
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<tr>
<td>4-5</td>
<td>COPD</td>
<td>4-5</td>
<td>4-5</td>
<td>(3 to 4)</td>
<td>(3 to 4)</td>
</tr>
<tr>
<td>5-7</td>
<td>Diarrhoea</td>
<td>5-7</td>
<td>5-7</td>
<td>(5 to 5)</td>
<td>(5 to 5)</td>
</tr>
<tr>
<td>6-9</td>
<td>Tuberculosis</td>
<td>6-9</td>
<td>6-9</td>
<td>(5 to 9)</td>
<td>(5 to 9)</td>
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<tr>
<td>7-11</td>
<td>Preterm birth complications</td>
<td>7-11</td>
<td>7-11</td>
<td>(7 to 9)</td>
<td>(9 to 11)</td>
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<tr>
<td>8-12</td>
<td>Lung cancer</td>
<td>8-12</td>
<td>8-12</td>
<td>(7 to 12)</td>
<td>(8 to 11)</td>
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<tr>
<td>9-14</td>
<td>Malaria</td>
<td>9-14</td>
<td>9-14</td>
<td>(7 to 13)</td>
<td>(7 to 13)</td>
</tr>
<tr>
<td>10-14</td>
<td>Road injury</td>
<td>10-14</td>
<td>10-14</td>
<td>(8 to 14)</td>
<td>(10 to 13)</td>
</tr>
<tr>
<td>11-15</td>
<td>Protein-energy malnutrition</td>
<td>11-15</td>
<td>11-15</td>
<td>(10 to 16)</td>
<td>(11 to 13)</td>
</tr>
<tr>
<td>12-16</td>
<td>Cirrhosis</td>
<td>12-16</td>
<td>12-16</td>
<td>(8 to 16)</td>
<td>(9 to 12)</td>
</tr>
<tr>
<td>13-17</td>
<td>Stomach cancer</td>
<td>13-17</td>
<td>13-17</td>
<td>(9 to 18)</td>
<td>(9 to 16)</td>
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<tr>
<td>14-18</td>
<td>Self-harm</td>
<td>14-18</td>
<td>14-18</td>
<td>(9 to 17)</td>
<td>(10 to 18)</td>
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<tr>
<td>15-20</td>
<td>Hypertensive heart disease</td>
<td>15-20</td>
<td>15-20</td>
<td>(10 to 18)</td>
<td>(11 to 17)</td>
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<tr>
<td>16-20</td>
<td>Neuropathic conditions</td>
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<td>16-20</td>
<td>(12 to 18)</td>
<td>(12 to 17)</td>
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<tr>
<td>17-22</td>
<td>Neonatal encephalopathy*</td>
<td>17-22</td>
<td>17-22</td>
<td>(13 to 17)</td>
<td>(15 to 18)</td>
</tr>
<tr>
<td>18-24</td>
<td>Hypertensive heart disease</td>
<td>18-24</td>
<td>18-24</td>
<td>(14 to 22)</td>
<td>(16 to 21)</td>
</tr>
<tr>
<td>19-26</td>
<td>Measles</td>
<td>19-26</td>
<td>19-26</td>
<td>(16 to 24)</td>
<td>(20 to 25)</td>
</tr>
<tr>
<td>21-26</td>
<td>Neonatal sepsis</td>
<td>21-26</td>
<td>21-26</td>
<td>(20 to 26)</td>
<td>(24 to 25)</td>
</tr>
<tr>
<td>22-28</td>
<td>Colorectal cancer</td>
<td>22-28</td>
<td>22-28</td>
<td>(19 to 26)</td>
<td>(23 to 28)</td>
</tr>
<tr>
<td>23-30</td>
<td>Meningitis</td>
<td>23-30</td>
<td>23-30</td>
<td>(18 to 26)</td>
<td>(24 to 30)</td>
</tr>
<tr>
<td>24-32</td>
<td>Other cardiovascular and circulatory</td>
<td>24-32</td>
<td>24-32</td>
<td>(17 to 26)</td>
<td>(22 to 31)</td>
</tr>
<tr>
<td>25-38</td>
<td>Rheumatic heart disease</td>
<td>25-38</td>
<td>25-38</td>
<td>(20 to 27)</td>
<td>(25 to 30)</td>
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<tr>
<td>26-44</td>
<td>Chronic kidney disease</td>
<td>26-44</td>
<td>26-44</td>
<td>(21 to 27)</td>
<td>(26 to 31)</td>
</tr>
<tr>
<td>27-50</td>
<td>Falls</td>
<td>27-50</td>
<td>27-50</td>
<td>(23 to 28)</td>
<td>(28 to 33)</td>
</tr>
<tr>
<td>28-55</td>
<td>Protein-energy malnutrition</td>
<td>28-55</td>
<td>28-55</td>
<td>(24 to 30)</td>
<td>(30 to 40)</td>
</tr>
<tr>
<td>29-62</td>
<td>Congenital anomalies</td>
<td>29-62</td>
<td>29-62</td>
<td>(25 to 30)</td>
<td>(30 to 60)</td>
</tr>
<tr>
<td>30-65</td>
<td>Colorectal cancer</td>
<td>30-65</td>
<td>30-65</td>
<td>(26 to 31)</td>
<td>(31 to 65)</td>
</tr>
<tr>
<td>31-72</td>
<td>Neonatal encephalopathy*</td>
<td>31-72</td>
<td>31-72</td>
<td>(27 to 32)</td>
<td>(32 to 72)</td>
</tr>
<tr>
<td>32-75</td>
<td>Neonatal sepsis</td>
<td>32-75</td>
<td>32-75</td>
<td>(28 to 33)</td>
<td>(33 to 75)</td>
</tr>
<tr>
<td>33-78</td>
<td>Meningitis</td>
<td>33-78</td>
<td>33-78</td>
<td>(30 to 35)</td>
<td>(35 to 78)</td>
</tr>
<tr>
<td>34-80</td>
<td>Rheumatic heart disease</td>
<td>34-80</td>
<td>34-80</td>
<td>(31 to 36)</td>
<td>(36 to 80)</td>
</tr>
<tr>
<td>35-82</td>
<td>Measles</td>
<td>35-82</td>
<td>35-82</td>
<td>(32 to 37)</td>
<td>(37 to 82)</td>
</tr>
<tr>
<td>36-84</td>
<td>Chronic kidney disease</td>
<td>36-84</td>
<td>36-84</td>
<td>(33 to 38)</td>
<td>(38 to 84)</td>
</tr>
</tbody>
</table>

*Communicable, maternal, neonatal, and nutritional disorders
Non-communicable diseases
Injuries

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US Mortality\(^1\)

4\(^{th}\) leading cause of death in US

Age-standardized death rates in US from COPD by sex 1999-2010\(^2\)

- Men: 57 -> 46.4 per 100K
- Women: 35.3 -> 36.4 per 100K
- Overall death rate slightly declining in US, \textit{though not for women!}

\(^1\)CDC website accessed Oct 2019 at: [www.cdc.gov/copd/data.htm](http://www.cdc.gov/copd/data.htm)
B. Percent change in age-standardized mortality rate from chronic obstructive pulmonary disease between 1980 and 2014, both sexes.
COPD: NATURAL HISTORY

- Everyone loses lung function
- Smokers lose lung function at different rates and most do not develop symptoms
- If one QUILTS smoking: Curve reverts to prior shape (rate of lung function loss reverts to that of a non-smoker), but lung function is NOT regained
COPD: Natural History

Postma, Bush, van den Berge. Lancet 2014; S0140-6736(14)60446-3

Personal smoking AND Maternal smoking

Figure 1: Risk factors for chronic obstructive pulmonary disease during the different stages of life and how they can affect the risk for the development of clinically apparent disease. FEV₁ = forced expiratory volume in 1 s. Any or all of a reduced starting point at birth, a failure to reach the normal plateau, and accelerated loss of function in adulthood mean that the threshold for respiratory symptoms and disability is reached earlier than normal. The extent of the effects of smoking varies between individuals and has been reported differently; therefore, the figure is a scheme to show the effects of smoking during the different stages in life.
Pathogenesis
Failure to divide: “old” Telomere length
Reduced local stem cells
Failure to “shut off”

Epithelial damage
Innate immune defence *
Adaptive immune response *

*Macros & neutros: Repeat activation & tissue destruction
*Repeat stimulation of T cells by T1 cytokines: aberrant B-cell proliferation, self-intolerance, & recurrent small airways inflammation

Lancet 2012;379-1341-51
Clin Interventions Aging 2013;8:1489-96
Frontiers Immunol 2014;5:1-7

*Brusselle GG, Joos GF, Bracke KR. Lancet 2011;378:1015-26 (excellent review of COPD immunobiology)
Oxidative Stress

SOD
Catalase
Vit E
Vit C
Glutathione

$O_2 \rightarrow O_2^-, H_2O_2, \cdot NO, HOCl$
(~2%)

PM$_{2.5}$

↑ FiO2 (~>0.6)

↓ FiO2 (hypoxia)

Endogenous inflammation

ROS
RNS

Rogers LK and Cismowski MJ. Cur Opin Tox 2018;7:37-43
Airflow obstruction is mediated by:

1. Airway inflammation and narrowing
2. Loss of elastic supporting tissue
3. Distortion of normal anatomy/geometry

Lancet 2012;379:1341-51
SYSTEMS CONCEPT OF COPD
How do many physicians think of COPD?

- Disability & Mortality
- Response to therapy (slower rate of decline & symptoms control)

- Not exercise intolerance, exacerbation frequency, psychosocial well-being, comorbid disease

THE Refined ABCD ASSESSMENT TOOL

- Spirometrically Confirmed Diagnosis
- Assessment of airflow limitation
- Assessment of symptoms/risk of exacerbations

Post-bronchodilator $\text{FEV}_1/\text{FVC} < 0.7$

<table>
<thead>
<tr>
<th>Grade</th>
<th>$\text{FEV}_1$ (% predicted)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GOLD 1</td>
<td>$\geq 80$</td>
</tr>
<tr>
<td>GOLD 2</td>
<td>$50-79$</td>
</tr>
<tr>
<td>GOLD 3</td>
<td>$30-49$</td>
</tr>
<tr>
<td>GOLD 4</td>
<td>$&lt; 30$</td>
</tr>
</tbody>
</table>

Moderate or Severe Exacerbation History

- $\geq 2$ or $\geq 1$ leading to hospital admission
- 0 or 1 (not leading to hospital admission)

Symptoms

- mMRC 0-1
- CAT $< 10$
- mMRC $\geq 2$
- CAT $\geq 10$

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# COPD Assessment Test (CAT™)

**CAT™ ASSESSMENT**

*For each item below, place a mark (x) in the box that best describes you currently. Be sure to only select one response for each question.*

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

**TOTAL SCORE:** *

Reference: Jones et al. ERJ 2009; 34 (3); 648-54.  
FIGURE 2.3
### MODIFIED MRC DYSPNEA SCALE

> PLEASE TICK IN THE BOX THAT APPLIES TO YOU  |  ONE BOX ONLY  |  Grades 0 - 4

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

---

\[a\] Fletcher CM. BMJ 1960; 2: 1662.

TABLE 2.5

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DYSPNEA IN COPD

Dynamic hyperinflation

CV dysfunx

Resp muscle dysfunx

Gas-exchange abnormalities

Chronic resp muscle activ

Respir Physio Neurobiol 2009;PMID 19450767
PA:
- Hyperinflation (>10 post ribs)
- Abrupt tapering of vascular markings
- Narrowed cardiac silhouette

Lateral:
- Increased A-P diameter
- Increased retrosternal airspace
- Flattened hemidiaphragms
DYSPNEA ON EXERTION

Minute Ventilation (L/min)

Lung Vol (L)

Vt = tidal volume
FRC = functional residual capacity
IC = inspiratory capacity
TLC = total lung capacity

Dynamic hyperinflation
FRC increases & IC decreases
SYSTEMIC MANIFESTATIONS
Systemic Effects & Comorbidities in COPD

- Anxiety/depression
- Cardiovascular disease
- Musculoskeletal
- Hypertension
- Diabetes

Lung cancer

Peripheral lung inflammation

Skeletal muscle weakness
Cachexia

Systemic inflammation
IL-6, IL-1β, TNF-α

Acute phase proteins
CRP
Serum amyloid A
Surfactant protein D

- Ischaemic heart disease
- Cardiac failure
- Osteoporosis
- Diabetes metabolic syndrome
- Normocytic anaemia
- Depression

© Material reprinted with permission of authors Barnes & Celli ERJ 2009;33:1165-85
SYSTEMIC MANIFESTATIONS OF COPD: WHO CARES?

- Certain systemic d/o’s occur w/ higher frequency in COPD than age-matched general population

- Treatment of COPD and/or associated d/o’s may affect outcomes

- Better global understanding of COPD
  - Impacts treatment choices
  - Impacts QoL
  - May improve mortality
CARDIOVASCULAR DISEASE & COPD
COPD & Cardiovascular Disease\textsuperscript{1,4}

- Reduced FEV1 $\rightarrow$ ↑ risk of MI
- COPD & CV, common risk: smoking

However, treating COPD in \textit{former smokers} may reduce cardiac death
- TORCH: Near significant, $p=0.052$\textsuperscript{2}
- UPLIFT: HR 0.86 (95\% CI, 0.75-0.99)\textsuperscript{3}

This indicates an \textit{association} between COPD and CV dz beyond that of smoking, though a \textit{causal} relationship between COPD and CV disease HAS NOT been shown

\textsuperscript{1}Heart 2012;98:1055-62
\textsuperscript{2}N Engl J Med 2007 Feb 22;356(8):775-89
\textsuperscript{3}Am J Respir Crit Care Med 2009;180(10):948-55
ECLIPSE

• Higher prevalence of co-morbidities in COPD

• Increased mortality with combined COPD and co-morbidity

  • Heart failure HR 1.9 (95%CI 1.3-2.9)
  • Isch Heart Dz HR 1.5 (1.1-2.0)
  • Heart Dz HR 1.5 (1.2-2.0)
  • Diabetes HR 1.7 (1.2-2.4)

• Cumulative risk with more co-morbidities

Miller J, et al. Respir Med 2013;PMID 23791463
COPD & Sudden Cardiac Death

Cumulative survival vs. follow-up (days)

- No COPD
- COPD without frequent exacerbations
- COPD with frequent exacerbations

Follow-up (days)

Cumulative survival

© Material reprinted with permission of publisher under license no. 4096800702969 via RightsLink/Copyright Clearance Center. Lahousse et al, Eur Heart J, 2015; 36: 1754-61
Effect on COPD when using cardiac drugs
**Beta Blockers & COPD**

- U Tenn\(^1\). Retro cohort: 166 BB & 246 non-BB
  - AECOPD OR 0.61 (CI 0.4-0.93) favor BB
  - AECOPD based on cardioselectivity... no diff

- 825 AECOPD in AL: Death OR 0.39 (CI, 0.14-0.99) w/ BB use (any)\(^2\)

- 2230 outpt COPD, Dutch: Death adj OR 0.68 (CI, 0.56-0.83) & AECOPD adj OR 0.71 (95% CI, 0.60-0.83)\(^3\)

- OPTIMIZE-HF, 722 COPD + sCHF: Dec’d mortality in COPD on BB (any)\(^4\)

- 4858 pt w/ COPD & MI, BB vs none at discharge, Swedish: Reduced mortality w/ BB use (any)\(^5\)

- *Caveat: BBs in O2-dependent COPD subjects (N=2249) associated w/ inc’d mortality (HR 1.19 [1.04-1.37])\(^6\)

---

\(^1\)Farland MZ et al. Ann Pharmacother 2013;PMID 23585645
\(^2\)Dransfield et al. Thorax 2008;PMID 17951276
\(^3\)Rutten et al. Arch Int Med 2010;PMID 20498416
\(^4\)Mentz et al. Am J Cardiol 2012;PMID 23200803
\(^5\)Andell et al. J Am Heart Assoc 2015;PMID 25854796
\(^6\)Ekstrom et al. AJRCCM 2013;PMID 23328521
\(^7\)Kuhn et al. Ch3 in Beta Blockers. Richards Ed. 2018
RENIN-ANGIOTENSIN SYSTEM

- ARB: protects smoked mouse lungs\(^1\)
- ACEi’s in COPD: augments LV fx, pulm vascular tone, and is anti-inflammatory\(^2\)

- Lovelace Smokers Cohort\(^3\):
  - 809 smokers W/O COPD,
  - Followed >3 yrs
  - ACEi decreased
    - FEV\(_1\) decline [OR 0.55 (0.33-0.93, p=0.03)]
    - incident COPD [OR 0.34 (0.15-0.78, p=0.03)]

---

1Podowski et al. J Clin Invest 2012;PMID 22182843
3Petersen et al. Chest 2014;PMID 24008986
Effect of COPD treatment on cardiovascular disease
COPD INHALED TX ON CV RISK

TORCH¹
- 6112 COPD, GOLD II+
- Near-significant reduction in CV death (p=0.052)

UPLIFT²
- 5993 COPD, GOLD II+
- CV death HR 0.86 (CI, 0.75-0.99)

²Am J Respir Crit Care Med 2009;180(10):948-55
WHAT DOES THIS MEAN???
Assess all COPD patients for cardiac dz (esp Groups B & D)

Controlled cardiac dz may improve COPD outcomes (& vice versa)

*Unexplained* dyspnea (group B) may herald occult cardiac disease
SKELETAL MUSCLE DYSFX

- disuse atrophy\(^1\)
- systemic inflammation\(^2\)
  - \(\uparrow\) NF-κB activation
  - \(\downarrow\) PPAR-γ activity,
  - \(\uparrow\) ROS
- Dec’d O2 consumption by myocytes\(^3\)
- Worse after AECOPD\(^4\)
- \(\uparrow\) mortality independent of FEV1 & smoking\(^5\)
  (think BODE)

- Pulm rehab: \(\uparrow\) exercise tol & \(\downarrow\) inflammation\(^6\)

---

1Man et al. Thorax 2003;58:665-9
3Degens et al. AJRCCM 2015:PMID 25581779
4Cote et al. Chest 2007;131:696-704
COPD AND LUNG CA

- Smokers lifetime risk\(^1\): 17.2% men, 11.6% women
  - Nonsmokers: ~1.3% both

- Airflow obstruction: 5X risk of lung CA\(^2\)

- Lung CA #1 cause of CA death worldwide\(^3\)-\(^5\)

- Genetics & epigenetics may increase risk of COPD and lung CA\(^6\)

\(^1\)Can J Pub Health 1994;PMID 7895211
\(^2\)Respir Med 2010;PMID 20226648
\(^3\)Cancer J Clin 2011;PMID 21296855
\(^6\)Lung Cancer 2015;PMID 26363803
3-4X likely to develop CA than non-COPD smokers

50-75% BMD loss
TNF-α, IL-18, IL-6
MMP-9
**Pulm rehab** may reduce falls

RR 1.28-1.8 across many large studies
Unrelated to steroids
TNF-α, IL-6, CRP

15-30% Functional capacity & QoL

High prevalence
Freq untx’d
IL-6
**Pulm rehab** improves depression/anxiety independent of dyspnea

THERAPEUTIC CONSIDERATIONS
**Treatment of stable COPD**

**INITIAL PHARMACOLOGICAL TREATMENT**

<table>
<thead>
<tr>
<th>Group A</th>
<th>Group B</th>
<th>Group C</th>
<th>Group D</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 or 1 moderate exacerbations (not leading to hospital admission)</td>
<td>A Bronchodilator</td>
<td>LAMA</td>
<td>LAMA or LAMA + LABA* or ICS + LABA**</td>
</tr>
</tbody>
</table>

- **Group A**: mMRC 0-1 CAT < 10
- **Group B**: mAIC 0-2 CAT ≥ 10
- **Group C**: LAMA
- **Group D**: LAMA or LAMA + LABA* or ICS + LABA**

*Consider if highly symptomatic (e.g. CAT > 20)
**Consider if eos ≥ 300

**Definition of abbreviations:** eos: blood eosinophil count in cells per microliter; mMRC: modified Medical Research Council dyspnea questionnaire; CAT™: COPD Assessment Test™.
PATIENT CONSIDERATIONS

- Cost
- Patient ability
  - Nebulizer vs inhaler(s)
  - Arthritis
  - Peak inspiratory flow
- Complexity
- Side effects

FIGURE 4.2
POOR INSPIRATORY FLOW

- Respiratory muscle weakness
- Hyperinflation
- Poor coordination

- In-check flow meter

<table>
<thead>
<tr>
<th>Device</th>
<th>Minimal</th>
<th>Optimal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Turbuhaler®/Flexhaler®</td>
<td>30</td>
<td>60</td>
</tr>
<tr>
<td>Easyhaler®</td>
<td>30</td>
<td>30</td>
</tr>
<tr>
<td>Diskus®</td>
<td>30</td>
<td>60</td>
</tr>
<tr>
<td>HandiHaler®</td>
<td>20</td>
<td>30</td>
</tr>
<tr>
<td>Ellipta®</td>
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<td>60</td>
</tr>
<tr>
<td>Aerolizer®</td>
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<td>65</td>
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<tr>
<td>Genuair®</td>
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<td>45</td>
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<tr>
<td>Breezhaler®</td>
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<tr>
<td>Spiromax®</td>
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<tr>
<td>Novolizer®</td>
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<td>50</td>
</tr>
<tr>
<td>NEXThaler®</td>
<td>35</td>
<td>35</td>
</tr>
</tbody>
</table>

Sanders MJ. Pulm med. 2017;1495867. PMID 29348936
Chronic anti-inflammatory agents

- Roflumilast
- Macrolide therapy
- Doxycycline
MEDICATION COST

- Identifying alternatives
  - E.g., Duonebs QID rather than a LAMA
  - Single inhalers or long-acting rather than multiple times a day
  - Demonstrating medical need (e.g., low PIFR)
**Medication Teaching**

- Incorrect inhaler technique is common
- Some groups may be more affected
  - Older
  - Low SE status

- Inhaler teaching with placebo devices may help
  - Improve sxs
  - Reduce exacerbations
OXYGEN THERAPY

- LTOT and NOTT\textsuperscript{1,2}
  - Severe resting hypoxemia or cor pulmonale
  - 15-18 hrs per day
  - Mortality benefit

- Exertional and/or mild resting hypoxemia\textsuperscript{3}
  - Likely no major benefit

\textsuperscript{1}Ann Intern Med 1980;93(3):391
\textsuperscript{2}Lancet 1981;1(8222):681
\textsuperscript{3}NEJM 2016;375:17:1617-27
NON-PHARM MANAGEMENT

- Pulm Rehab
  - Primary care referrals are low
  - Multiple benefits
    - Immediate; Long term only for those who keep it up
- Self-directed management (home-based)
- Pt education
- Smoking cessation
- Vaccinations
- Hypercapnia- home NIV
- Nutrition
- Palliative care

2 Eur Respir J. 2005;26(4):630
3 Respir Res. 2005;6:54
4 Cochrane Database Syst Rev 2011;(10):CD005305
5 Eur Respir Rev 2010;19(115):24-9
Overview of various therapies used to treat patients with COPD and emphysema worldwide. Note that all therapies are not approved for clinical care in all countries. Additionally, the effects of BLVR on survival or other long term outcomes or comparison to LVRS are unknown.

Advanced COPD

- emphysema predominant phenotype with severe hyperinflation
  - large bulla
    - bullectomy
  - heterogeneous emphysema
    - no large bulla
    - LVRS BLVR (EBV, LVRC, VA)
  - homogeneous emphysema
    - not candidate for bullectomy, BLVR or LVRS
    - lung transplant

Definition of Abbreviations: BLVR, Bronchoscopic Lung Volume Reduction, EBV, endobronchial Valve, LVRS, Lung volume reduction surgery, LVRC, Lung volume reduction coil, VA, Vapor ablation

* at some but not all centers

FIGURE 4.5

© 2019 Global Initiative for Chronic Obstructive Lung Disease
A1AT Augmentation

- Replacement therapy decreases the rate of lung fx loss in subjects with severely reduced AAT levels (CT density)\(^1,2\)

- Unclear if replacement therapy may help in pts with mild/moderate reductions in AAT subjects

EVERYONE WITH COPD SHOULD BE TESTED:

- Alpha-1-antitrypsin Phenotype

---

1 Chapman et al. Lancet 2015;386(991):360-8
What's new in exacerbations?

- Azithro-
  - Used for outpt w/ ongoing exacerbations despite max therapy

- 301 AECOPD, placebo vs azithro x3 mos

Outcomes: treatment failure (intensification, step-up in care, readmission, mortality)

- Azithro group:
  - Lower high-dose steroids or abx need
  - Lower ICU admission

Vermeersch K et al. AJRCCM 2019; PMID: 31046405
PHENOTYPING
CONCEPTS IN PHENOTYPING

- Spirometry alone fails to identify who would benefit most from intervention
- General guidelines fail in many pts
- Optimal strategy to define pts is unclear
- Understanding inter-relationships of the following domains may improve clinical outcomes:
  - Inflammation
  - Clinical
  - Genetic
  - Physiologic
  - Radiographic
Clinical Characteristics
Women, advanced age

Comorbidities

Systemic inflammation

Physiologic
Rapid FEV1 decliners
Airtrapping

Proposed COPD Phenotypes

Frequent Exacerbators

Radiographic
Heterogenous Dz*
Small airways

*Ann Thoracic Surg 2006;82:431-43

Am J Respir Crit Care Med 2010;182:598–604
CLINICAL PHENOTYPES EXAMPLES

- Asthma-COPD overlap
  - Spirometry
  - T2-biomarkers
  - Sxs

- Chronic bronchitis (?bronchiectasis)
  - Imaging
  - Sputum production

- Lung fibrosis
  - Referral to ILD clinic

- Emphysema-predominant
  - Endobronchial interventions
UCD Comprehensive COPD Clinic

- Registry
  - >250 subjects
  - Captures multidimensional data longitudinally
    - Symptoms
    - Reported exacerbations
    - Comorbidities
    - Serologic biomarkers, e.g., T2 inflammatory biomarkers
    - Radiographic data
    - Lung fx
    - Therapies
    - Novel biomarkers, ?breath, cheek swabs
Patient-centered goals
• Decrease hospitalizations
• Decrease AECOPD
• Improve QoL

Institutional Goals
• Excellence in clinical care
• Improve COPD research
• Foster quality education

COPD
• Asthma-COPD Overlap (UCAN)
• Adult CF/BCT
• A1AT Deficiency
• Bronchial Thermoplasty

Clinical Care
• Comprehensive Care
• Primary COPD
• Co-morbidities
• Standard & Advanced therapy
• Coordination by RRT case managers w/ PCPs
• Patient/family education
• Specialty Referral

Education
• Patients & families
• Medical Students
• Physician Trainees
• RRT case managers & clinic coordinators

Research
• Sample collection for biorepository
• Database development
• Clinical Trials

Thoracic Surgery
Smoking Cessation
Pulm Rehab

Collaborators & Industry
UC DAVIS COLLEGE OF ENGINEERING
UC DAVIS HEALTH SYSTEM
CLINICAL AND TRANSLATIONAL SCIENCES CENTER
WHO ARE WE? UC DAVIS COMPREHENSIVE COPD CLINIC
NOVEL DIRECTIONS IN COPD
Asthma & COPD breath classification

Volatile metabolic compound analysis of breath was able to correctly classify:

- Asthma from control 75% of the time
- Controls from COPD
- Subjects taking omalizumab (anti-IgE) from controls 70% of the time

Principle component analysis on clinical subgroups: Controls vs COPD not taking tiotropium

INFLAMMATORY MARKERS IN BREATH

MICRO PC SAMPLER FOR ENVIRONMENTAL VOC EXPOSURE

- Programmable sampling flow strength and times
- Temperature and humidity sensor, GPS
- Rechargeable battery via USB connection

McCartney MM et al. ACS Sensors 2017;2(8):1167-74
Fung AG et al. ACS Sensors. 2019 May 24;4(5):1358-1364
MICRO PC SAMPLER FOR ENVIRONMENTAL VOC EXPOSURE

<table>
<thead>
<tr>
<th>#</th>
<th>Compound</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>fenchene</td>
</tr>
<tr>
<td>2</td>
<td>benzaldehyde</td>
</tr>
<tr>
<td>3</td>
<td>limonene</td>
</tr>
<tr>
<td>4</td>
<td>eucalyptol</td>
</tr>
<tr>
<td>5</td>
<td>benzyl alcohol</td>
</tr>
<tr>
<td>6</td>
<td>2-methyldecane</td>
</tr>
<tr>
<td>7</td>
<td>ocimene</td>
</tr>
<tr>
<td>8</td>
<td>undecane</td>
</tr>
<tr>
<td>9</td>
<td>nonanal</td>
</tr>
<tr>
<td>10</td>
<td>ethylene glycol monohexyl ether</td>
</tr>
<tr>
<td>11</td>
<td>menthone</td>
</tr>
<tr>
<td>12</td>
<td>menthol</td>
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<tr>
<td>15</td>
<td>nerol</td>
</tr>
<tr>
<td>16</td>
<td>cuminal</td>
</tr>
</tbody>
</table>

Fung AG et al. ACS Sensors. 2019 May 24;4(5):1358-1364
KEY POINTS

- Obtain PFTs/spirometry
- Assess symptoms and consider CV disease
- Understand that COPD co-exists with a number of disorders
- Check an alpha-1-antitrypsin phenotype
- Review inhaler technique, medication use (consider PIF)
- Refer for pulmonary rehabilitation
- Consider azithro for AECOPD
THANK YOU!

mschivo@ucdavis.edu