COPD and Comorbidities

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Overview

I will be discussing:

- Smoking and COPD in China
- The TASCS study
- What are comorbidities?
- What is their importance in COPD?
- What is the relationship between comorbidities and COPD and/or systemic inflammation? New ‘omes’ (diseasome, comorbidome)

I will not be discussing:

- Lung cancer
COPD
COPD is a leading cause of death worldwide – all ages 2004

WHO global burden of disease report, 2004
COPD risk factors in China

- Smoking
- Biomass fuels
- TB
- Air pollution
Smoking Prevalence in China

China is the greatest consumer of tobacco in the world.

China is the greatest producer of tobacco in the world

Fang X et al. Chest; 139: 920-929
Chromatin remodeling and gene expression

Barnes PJ. Chest 2006; 129: 151-155
Prevalence of COPD

Males 12.4%
Females 5.1%

Globally varies from 6 to 19% (BOLD)

China

Leading Chronic Diseases in China (DALYs)

Fang X et al. Chest 2011; 139: 920-929
COPD comprehensive treatment

Smoking cessation
Pharmacologic treatment
Pulmonary rehabilitation
Vaccination
LVRS / transplantation
Current drug treatment recommendations

GOLD stage 1 and 2 - bronchodilators. SABAs, LABAs, LAMAs, theo
GOLD stage 3 and 4 - add ICS. Usually combination ICS/LABA
Increasing evidence that ICS/LABA + LAMA effective
LABA + LAMA provides superior bronchodilatation
Limited anti-inflammatory efficacy of ICS in COPD (in contrast to asthma)

In conclusion, the reports from randomized trials and the meta-analysis that inhaled corticosteroids reduce COPD exacerbation rates are the result of improper statistical analysis techniques. The only two studies that used the correct statistical approach found insignificant effects with these drugs.

Increasing evidence for pneumonia in ICS treated patients

Anti-inflammatory effects of corticosteroids

Barnes PB and Adcock IM. Lancet 2009; 373-1905-17
Reduced histone deacetylase in COPD - Mechanism for corticosteroid resistance

Barnes PB. Chest 2006; 129: 151-155
Strategies to restore HDAC functions

Barnes PB. Chest 2006; 129: 151-155
Effect of theophylline and Flu on reactive nitrogen species

Hirano T et al. Thorax 2006; 61: 761-766
Effect of theophylline and Flu on inflammatory cells in COPD induced sputum

Before and after 4 weeks of Theo 400mg/day or Flu 400ug/day

Hirano T et al. Thorax 2006; 61: 761-766
Effect of theophylline and Flu on IL-8 in COPD induced sputum

Hirano T. Thorax 2006; 61: 761-766
Effect of theophylline and Dexamethasone on HDAC activity in alveolar macrophages

Theophylline

Bronchodilator at high plasma concentrations
  Non-selective phosphodiesterase inhibitor
  ↑cAMP through inhibition of PDE 3 and PDE 4
  ↑cGMP through inhibition of PDE 5

Anti-inflammatory effects at low plasma concentrations
  ↓infiltration of eos and CDE4+ cells after Ag challenge
  ↓neutrophils and IL 8 in sputum in COPD
  ↑HDAC activity
Low dose steroid/low dose theophylline study

Suggested in major editorials

Barnes PJ, Thorax 2006
Rabe and Hiemstra, Am J Respir Crit Care Med, 2010

TASCS
COPD Comorbidities
Importance of comorbidities and inflammation status

Prognosis and disability poorly explained by the FEV1

Multidimensional assessment indices
- BODE Index (BMI, FEV1, dyspnea, exercise capacity)
- ADO Index (age, dyspnea, FEV1)
- DOSE Index (dyspnea, FEV1, smoking status, exacerbations)

Puhan MA et al. Lancet 2009
Jones RC et al. Am J Respir Crit Care Med 2009
Importance of comorbidities

Comorbidities influence

Quality of life
Mortality
Disease management
Treatment outcomes (eg. effectiveness of pulmonary rehabilitation)

? Include comorbidities, inflammometry, clinical phenotypes, genotypes

Divo M et al. Am J Respir Crit Care Med 2012; 186: 155-161
Crisafulli E et al. Thorax 2008; 63: 487-492
Comorbidity - definition

A concomitant but unrelated pathological or disease process

_The American Heritage Medical Dictionary, 2007_

Pertaining to a disease or other pathological process that occurs simultaneously with another

_Dorland’s Medical Dictionary, 2007_

1. to indicate a medical condition existing simultaneously but independently with another condition in a patient
2. to indicate a medical condition in a patient that causes, or is otherwise related to another condition in the same patient (non-standard definition – less well accepted)

_Wikipedia_
Multiple components of COPD

- Bronchitis & Bronchiolitis
- Emphysema
- Airway inflammation
- Systemic Inflammation

Symptoms
- Exercise tolerance
- HRQL
- ECOPD
- Prognosis

Systemic effects of COPD
- Weight loss (cachexia)
- Skeletal muscle dysfunction
- Cardiovascular disease
- Others
  - Osteoporosis
  - Depression & Fatigue
  - Cancer

Agusti A et al. Am J Respir Crit Care Med 2011; 183; 1129-1137
Causal relation between smoking, COPD, comorbidities and systemic inflammation?

Smoking → COPD → Systemic Inflammation

Comorbidities - Extrapulmonary manifestations of COPD or part of chronic systemic inflammatory syndrome?
Questions

Is there evidence of a ‘spillover’ from the lungs to the systemic circulation? (Note surfactant protein D)
Does systemic inflammation influence the course of COPD?
Are different COPD phenotypes associated with different comorbidities?
Is there a genetic link between COPD, comorbidities and/or systemic inflammation?
Prevalence of comorbidities in COPD

20,292 subjects ARIC and CHS studies (cardiovascular studies)
Spirometry available
Comorbid disease at baseline
5-year follow-up

Multinomial logistic regression predicting presence of comorbid diseases

<table>
<thead>
<tr>
<th>Gold category</th>
<th>Comorbid disease</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 or 4</td>
<td></td>
<td>1.8</td>
<td>2.9</td>
<td>3.5 (1.9-6.4)</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>1.4</td>
<td>2.4</td>
<td>3.2 (2.2-4.6)</td>
</tr>
<tr>
<td>1</td>
<td></td>
<td>1.1</td>
<td>1.4</td>
<td>1.0 (0.7-1.5)</td>
</tr>
<tr>
<td>0</td>
<td></td>
<td>1.3</td>
<td>2.1</td>
<td>3.6 (2.7-4.9)</td>
</tr>
<tr>
<td>Normal</td>
<td></td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
</tbody>
</table>

Odds ratios adjusted for age, sex, race, smoking, education level and BMI

Adapted from: Mannino DM et al. Eur Respir J 2008; 32: 962-969
Multivariate regression predicting diabetes, hypertension and CVD

<table>
<thead>
<tr>
<th>GOLD category</th>
<th>Diabetes</th>
<th>Hypertension</th>
<th>CVD</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 or 4</td>
<td>1.5 (1.1-1.9)</td>
<td>1.6 (1.2-1.9)</td>
<td>2.4 (1.9-3.0)</td>
</tr>
<tr>
<td>2</td>
<td>1.4 (1.2-1.6)</td>
<td>1.4 (1.3-1.6)</td>
<td>2.2 (1.9-2.5)</td>
</tr>
<tr>
<td>1</td>
<td>0.9 (0.8-1.1)</td>
<td>1.1 (0.9-1.2)</td>
<td>1.7 (1.5-1.9)</td>
</tr>
<tr>
<td>0</td>
<td>1.4 (1.1-1.6)</td>
<td>1.2 (1.1-1.3)</td>
<td>2.4 (2.1-2.8)</td>
</tr>
<tr>
<td>Normal</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

Odds ratio adjusted for age, sex, race, smoking, education level and BMI

Adapted from: Mannino DM et al. Eur Respir J 2008; 32: 962-969
SGQR in COPD and comorbidities

COPD, comorbidities and HRQL

Patients with COPD in general practice
  COPD HRQL (SF-36) impaired in all domains
  COPD significantly and independently associated with
    - physical functioning
    - vitality
    - general health
  Comorbidities associated with
    - social functioning
    - mental health
    - emotional problems
    - bodily pain
Mortality in TORCH

- Respiratory: 35%
- Cardiovascular: 27%
- Cancer: 21%
- Other: 10%
- Unknown: 7%
Presence of comorbidities predict death within 5 years

COPD in-hospital mortality – effect of comorbidities

COPD subtypes

342 COPD patients assessed 3 months after discharge for first hospitalisation, then followed for 5 years

3 groups identified by cluster analysis

- Group 1 – severe obstruction (FEV1 38% pred)
- Group 2 – mild to moderate obstruction (FEV1 63% pred)
- Group 3 – FEV1 58% pred with obesity, CVD, diabetes, systemic inflammation

Cluster analysis of COPD subtypes

Defining a ‘comorbidome’

1664 patients with COPD – mean FEV1 47%pred.
Prospective study – follow-up for a median of 51 months
40% of the patients died
79 comorbidities identified
12 predicted mortality
COTE index developed
Associated with increased risk of death

Divo M et al. Am J Respir Crit Care Med 2012; 186: 155-161
The ‘comorbidome’ and risk of mortality

Divo M et al. Am J Respir Crit Care Med 2012; 186: 155-161
What is systemic inflammation?

Definition – the presence of inflammatory markers (cytokines, cells or products of inflammation) in the systemic circulation

Heterogeneity – which markers? Importance of individual markers or clusters of markers?

Stability – how variable are the markers over time? Is there clinical information in the variability?
Association between COPD and systemic inflammation

Systematic review and meta-analysis
- 14 studies included in total
- Patients with stable COPD
- Systemic markers included CRP, fibrinogen, leucocytes, TNF-α, IL-6, IL-8

Limitations:
- Sampling and analysis not standardised
- Heterogeneity of the sample populations

Gan WQ et al. Thorax 2004; 59: 574-580
Association between COPD and systemic inflammation

Gan WQ et al. Thorax, 2004; 59: 574-580
Inflammatory biomarkers and comorbidities

8656 patients with COPD from 2 Danish populations (FEV1/FVC <0.7)
5 year follow-up
Three baseline inflammatory markers measured (C-reactive protein, fibrinogen, leucocyte count)
Recorded admissions for IHD, myocardial infarction, heart failure, type 2 diabetes, lung cancer, pneumonia, pulmonary embolism, hip fracture and depression.

Thomsen M et al. Am J Respir Crit Care Med 2012; 186: 982-988
Effect of biomarkers on 5-year risk

Thomsen M et al. Am J Respir Crit Care Med 2012; 186: 982-988
Effect of biomarkers on 5-year risk

Thomsen M et al. Am J Respir Crit Care Med 2012; 186: 982-988
Effect of biomarkers on 5-year risk

Lung cancer

Pneumonia

Thomsen M et al. Am J Respir Crit Care Med 2012; 186: 982-988
Systemic inflammation and clinical outcomes in COPD

ECLIPSE Study
1775 COPD patients (FEV1 48% pred), 297 smokers, 201 non-smoking controls
Six biomarkers measured (WBC, CRP, IL-6, IL-8, fibrinogen, TNF-α)
Biomarkers at baseline in nonsmokers, smokers with normal lung function and COPD patients
Stability of systemic inflammatory biomarkers over 12 months


16% Persistent systemic inflammation
30% No systemic inflammation
Network of systemic inflammatory response in nonsmokers, smokers with normal lung function and COPD patients

# Associations with persistent systemic inflammation (logistic regression)

<table>
<thead>
<tr>
<th>Demographics and clinical data</th>
<th>Odds Ratio (95%CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI</td>
<td>1.125 (1.063, 1.190)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Current Smoking</td>
<td>2.228 (1.471, 3.375)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SGRQ-C</td>
<td>1.017 (1.004, 1.030)</td>
<td>&lt;0.012</td>
</tr>
<tr>
<td>FEV1 %pred</td>
<td>0.975 (0.956, 0.995)</td>
<td>&lt;0.014</td>
</tr>
</tbody>
</table>

Clinical associations with persistent systemic inflammation

Significantly higher in patients with persistent systemic inflammation (over 3 years)
- All cause mortality
- Annual rate of COPD exacerbations

Lack of association with persistent systemic inflammation
- Rate of FEV1 decline
- Weight loss
- Occurrence of new cardiovascular events

Effect of Statins and ACE Inhibitors on Morbidity and Mortality in COPD

Retrospective nested case control study

ARB = angiotensin receptor blocker

Mancini GBJ et al. J Am Coll Cardiol 2006; 47: 2554-60
Results similar if steroid users are included
Effect of comorbidities on pulmonary rehabilitation

Only osteoporosis affected success rate (6MWD)

Crisafulli E et al. Eur Respir J 2010; 36: 1042-1048
Summary

COPD is strongly associated with comorbidities
The comorbidities influence
- quality of life
- mortality
- ? treatment outcomes

Any treatment algorithm for COPD needs to include diagnosis and management of comorbidities
More research is needed to see if
- treatment of COPD improves comorbidities
- treatment of comorbidities improves COPD
- treatment of systemic inflammation improves both
Comprehensive treatment options

Treat COPD to improve comorbidities?
- LAMA (Uplift) improves cardiac mortality
- ICS/LABA improves arterial stiffness

Treat comorbidities to improve COPD
- Little evidence

Treat systemic inflammation to treat both?
- some evidence for statins and ACE inhibitors - RCTs needed
Effect of inflammatory biomarkers on 5 year risk of comorbidities

Thomsen M et al. Am Respir Crit Care Med 2012; 186; 982-988
Exacerbations and systemic inflammation

Cazzola M et al. Trends in Pharmacological Sciences, 2007
Comorbidities of COPD

Fabbri LM et al. Eur Respir J 2008; 31: 204-212
Logistic regression for persistent systemic inflammation (2+ biomarkers at 2 visits over 12 months)

<table>
<thead>
<tr>
<th>Demographics and clinical data</th>
<th>Odds Ratio (95% CI)</th>
<th>p-value</th>
<th>AUC for Model</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs.)</td>
<td>1.045 (1.014, 1.077)</td>
<td>0.004</td>
<td></td>
</tr>
<tr>
<td>Female vs. Male</td>
<td>0.645 (0.383, 1.085)</td>
<td>0.098</td>
<td></td>
</tr>
<tr>
<td>BMI kg/m²</td>
<td>1.125 (1.063, 1.190)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Fat free mass index, kg/m²</td>
<td>0.979 (0.866, 1.106)</td>
<td>0.728</td>
<td></td>
</tr>
<tr>
<td>Current smoker vs. Former smoker</td>
<td>2.228 (1.471, 3.375)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Smoking, pack-years</td>
<td>1.004 (0.997, 1.011)</td>
<td>0.217</td>
<td></td>
</tr>
<tr>
<td>Chronic bronchitis</td>
<td>0.929 (0.624, 1.384)</td>
<td>0.717</td>
<td></td>
</tr>
<tr>
<td>mMRC Dyspnea Score</td>
<td>0.949 (0.756, 1.191)</td>
<td>0.65</td>
<td></td>
</tr>
<tr>
<td>SGRQ-C Total Score</td>
<td>1.017 (1.004, 1.030)</td>
<td>0.012</td>
<td></td>
</tr>
<tr>
<td>Exacerbation rate (prior year)</td>
<td>1.097 (0.956, 1.260)</td>
<td>0.187</td>
<td></td>
</tr>
<tr>
<td>ICS Use</td>
<td>1.354 (0.850, 2.159)</td>
<td>0.202</td>
<td></td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>0.714 (0.470, 1.085)</td>
<td>0.114</td>
<td></td>
</tr>
<tr>
<td>Statin Use</td>
<td>0.899 (0.576, 1.403)</td>
<td>0.638</td>
<td></td>
</tr>
<tr>
<td>Physiology and imaging</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FEV1% Predicted</td>
<td>0.975 (0.956, 0.995)</td>
<td>0.014</td>
<td></td>
</tr>
<tr>
<td>FEV1 Reversibility</td>
<td>0.999 (0.987, 1.011)</td>
<td>0.841</td>
<td></td>
</tr>
<tr>
<td>FEV1/FVC (%)</td>
<td>1.000 (0.972, 1.028)</td>
<td>0.977</td>
<td></td>
</tr>
<tr>
<td>6MWD (m)</td>
<td>0.998 (0.997, 1.000)</td>
<td>0.13</td>
<td></td>
</tr>
<tr>
<td>%LAA</td>
<td>0.987 (0.965, 1.008)</td>
<td>0.219</td>
<td></td>
</tr>
</tbody>
</table>

Statistically significant factors are highlighted in bold. For further explanations, see text.

doi:10.1371/journal.pone.0037483
Exacerbations
The postprandial session

Knowing that his post-lunch fatigue was destined to strike, Larry wore his head-mounted airbag.