Prevention and treatment of acute exacerbations of COPD

Prof. Laurent P Nicod
Service de pneumologie
CHUV-Lausanne-CH

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COPD EXACERBATION

“is an event in the natural course of the disease characterised by a change in the patient’s baseline dyspnoea, cough and/or sputum that is acute in onset, beyond usual day-to-day variation, and may warrant a change in regular medication in a patient with underlying COPD.”
COPD EXACERBATIONS

From Wedzicha, JA, Seemungal T Lancet 2007
Consequences Of COPD Exacerbations

- Negative impact on quality of life
- Accelerated lung function decline
- Increased economic costs
- Increased Mortality

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ASSOCIATION OF COPD SEVERITY AND EXACERBATION FREQUENCY

(2,138 patients in the ECLIPSE cohort study)

Differential diagnosis to COPD exacerbations

- Pneumonia
- Right heart failure or arrhythmias
- Pulmonary embolism
- Spontaneous pneumothorax
- Inappropriate oxygen administration
- Drugs (hypnotics, tranquillisers, diuretics, etc.)
- Poor nutritional stage
- End-stage respiratory disease (fatigue of respiratory muscles, etc.)
EXACERBATION RECOVERY TIME

Donaldson et al. AJRCCM 2005
Outcomes after oral Prednisolone for COPD exacerbations (40 mg/d for 10 days)

Probability to \textit{remain recidive free in the next 30 days}

Short term (5days) vs conventional (14 days) systemic steroids therapy in AECOPD: the reduce trial

Short term group had:
- 65% reduction in steroids
- shorter length of stay: 8 versus 9 days
- no increase in recurrence of exacerbation or mortality

Leupi et al JAMA 2013;309:2223
Major Triggers of COPD exacerbations

- **Bacterial** predominant
- **Eosinophil** predominant
- **Viral** predominant
- **Pauci** inflammatory

Mona Bafadhel et al. AJRCCM 2016
Dysbioses during COPD exacerbations correlate with increase in strains phylogenetically related to pasteurellaceae.

Enterobacteriaceae

Pasteurellaceae (e.g. Haemophilus)

Pseudomonadaceae, Moraxellaceae

Delta-proteobacteria

Beta-proteobacteria

R = 0.5-0.8
BH-adj p < 0.05
% RECOVERY OF COPD EXACERBATIONS AT 3 WEEKS WITH and WITHOUT ANTIBIOTICS

Anthonisen et al Ann Intern Med 1987

Mean FEV1 at 33.9% predicted

Major symptoms:
1) dyspnea
2) increased sputa
3) purulent sputa

Bar chart showing:
- Type 1: 3 major symptoms
- Type 2: 2 major symptoms
- Type 3: 1 major symptom, 1 minor symptom

Comparison between Placebo and Antibiotic groups.
Antibiotics for AECOPD: Risk Stratification

MILD
Only 1 of the 3 cardinal symptoms:
- Increased dyspnea
- Increased sputum volume
- Increased sputum purulence

- No antibiotics
- Increased bronchodilator
- Symptomatic therapy
- Monitoring of symptoms

MODERATE OR SEvere
At least 2 of the 3 cardinal symptoms:
- Increased dyspnea
- Increased sputum volume
- Increased sputum purulence

Uncomplicated COPD
No risk factors:
- Age <65 years
- FEV1 >50% predicted
- <2 exacerbations/year
- No cardiac disease

- Advanced macrolide (azithromycin, clarithromycin)
- Cephalosporin (cefuroxime, cefpodoxime, cefdinir)
- Doxycycline
- Trimethoprim–sulfamethoxazole
- If recent antibiotic exposure (<3 months), use alternative class

Complicated COPD
1 or More risk factors:
- Age 65 years
- FEV1 50% predicted
- >2 exacerbations/year
- Cardiac disease

- Fluoroquinolone (moxi, gemi, levofloxacin)
- Amoxicillin–clavulanate
- If at risk for Pseudomonas, consider ciprofloxacin and obtain sputum culture
- If recent antibiotic exposure (<3 months), use alternative class

Worsening clinical status or inadequate response in 72 hrs

Reevaluate
Consider sputum culture

Exacerbation free interval in patients with AECOPD successfully treated with antibiotic (amoxicillin/clavulanate) at Days 9 to 11.

<table>
<thead>
<tr>
<th>Type of exacerbation</th>
<th>Abtt</th>
<th>Placebo</th>
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<tbody>
<tr>
<td>Type I</td>
<td>40 (25.3)</td>
<td>45 (29.6)</td>
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<tr>
<td>Type II</td>
<td>81 (51.3)</td>
<td>72 (47.4)</td>
</tr>
<tr>
<td>Type III</td>
<td>37 (23.4)</td>
<td>35 (23.0)</td>
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Amox/clav: 233 days  
Placebo: 166 days  
P=0.015

Carl Llor et al
AJRCCM 201;186:716,
INHALED ANTIBIOTICS (COLISTIN) REDUCE FEV1 DECLINE IN COPD COLONIZED WITH PSEUDOMONAS

Open study after an initial follow up of 9 visits before start of colistin, and after for more than one year, in 18 COPD colonized with pseudomonas

<table>
<thead>
<tr>
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<th>Precolistin</th>
<th>Post-colistin</th>
<th>P-value</th>
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<tbody>
<tr>
<td>FEV₁, mL (range)</td>
<td>1070 (350–1950)</td>
<td>1020 (350–1900)</td>
<td>0.400</td>
</tr>
<tr>
<td>Decline in FEV₁, mL/year (range)</td>
<td>104 (25–325)</td>
<td>44 (~100 to 280)</td>
<td>0.035</td>
</tr>
<tr>
<td>FVC, L (range)</td>
<td>2.0 (1.0–3.6)</td>
<td>1.9 (1.0–3.3)</td>
<td>0.295</td>
</tr>
<tr>
<td>Decline in FVC, mL/year (range)</td>
<td>110 (0–500)</td>
<td>48 (~200 to 160)</td>
<td>0.033</td>
</tr>
<tr>
<td>Frequency of admission, n/year (range)</td>
<td>1.1 (0.1–7)</td>
<td>0.84 (0.0–4)</td>
<td>0.493</td>
</tr>
<tr>
<td>Quality of life</td>
<td>3.6</td>
<td>6.2</td>
<td>0.001</td>
</tr>
</tbody>
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Overall decrease in lung function decline and improved quality of life

D.P. Steinfort et al Internal Medicine Journal 37 (2007) 495
Frequence of COPD severe exacerbations* and mortality

Survival probability

- Absence of exacerbations
- 1–2 exacerbations*
- ≥ 3 exacerbations*

Lenght in months

- p < 0.0002
- p = 0.069

n = 304

* exacerbation leading to hospitalisation

Soler-Cataluña et al. Thorax 2005
TORCH – Causes of Death

- Lung: 36%
- Cardiovascular: 27%
- Tumor: 22%
- Unknown: 6%
- Other: 10%

LP McGarvey et al., Thorax 2007;62:411-5
COPD EXACERBATION FREQUENCY AND MYOCARDIAL INFARCTION INCIDENCE

Exacerbations (Prescriptions of Antibiotics and Steroids per year)

Myocardial Infarction (per 100 patient per year)

BIOMARKERS AT COPD EXACERBATIONS WITH AND WITHOUT ISCHEMIC HEART DISEASE

Patel et al AJRCCM 2013
Factors associated with change in COPD Exacerbation frequency

REDUCED SYSTEMIC INFLAMMATION IN COPD changing from Frequent to Infrequent exacerbators (CRP, FIBRINOGEN, CCL18/PARC)
CRP, WBC and FIBRINOGEN FOR EXACERBATION PREDICTION

Thomsen et al
JAMA 2013
## Therapeutic Options: COPD Medications

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<th>Beta₂-agonists</th>
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<td>Short-acting beta₂-agonists</td>
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<td>Long-acting beta₂-agonists</td>
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<th>Anticholinergics</th>
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<td>Short-acting anticholinergics</td>
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<td>Long-acting anticholinergics</td>
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**Combinations** of very long-acting beta₂-agonist + anticholinergic

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<th>Inhaled corticosteroids</th>
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<td>alone or combined</td>
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<tr>
<th>Azithromycine</th>
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<th>Systemic corticosteroids</th>
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<th>Phosphodiesterase-4 inhibitors</th>
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FEV1 changes with fluticasone propionate (ICS) alone or combined with salmeterol (LABA) for COPD

P Calverey and Torch invest. NEJM 2007;356:775
Reduced frequency of moderate and severe COPD exacerbations with ICS and LABA

Mean number of exacerbations / year

- Placebo: 1.13
- Salmeterol: 0.97* (25% reduction)
- Fluticasone: 0.93*
- Salmeterol (LABA): 0.85**

* p < 0.001 vs placebo; †p = 0.002 vs SALM; ‡p = 0.024 vs FP

Fluticasone: 500ug bid

P Calverey and Torch invest. NEJM 2007;356:775
Adjusted rate of hospitalisations for pneumonia according to the doses of inhaled steroids (ICS)

- Low = (fluticasone <500μg/jour)
- Medium = (fluticasone 500–999 μg/jour)
- High = (fluticasone > 1000μg/jour)

Données de Ernst et al.46
1. Price et al. Prim Care Respir J 2012; 21
2. Ernst et al. Am J Respir Crit Care Med 2007
Profil of FEV1 with tiotropium (LAMA) and olodaterol (LABA) compared to each in monotherapy for COPD

Values observed after 6 weeks

FEV1 at peak (338 ml différence Compared to placebo) at 3 hours

Residual difference of FEV1 : 207 ml (compared to placebo)

* p<0.0001 pour l'association à dose fixe tiotropium + olodaterol vs monothérapies et placebo

Long acting Bêta-2-agonists/
Long acting muscarinic antagonists (LABA/LAMA)

- indacatérol/glycopyrronium (Ultibro Breezhaler)
- vilantérol/uméclidinium (Anoro Ellipta)
- olodatérol/tiotropium (Spiolto Respimat)
Effects of indacaterol (LABA) and glycopyrronium (LAMA) versus LAMAs alone, on RATE of COPD EXACERBATIONS

- 12% reduction, p=0.038 (primary endpoint)
- 10% reduction, p=0.096 (secondary endpoint)

Annual rate of moderate or severe COPD exacerbations

Indac et glycopyr. 110/50 µg q.d.
Glycopyrronium 50 µg q.d.
Open-label tiotropium 18 µg q.d.

Indecaterol (LABA) and glycopyrronium (LAMA) are superior to salmeterol (LABA) and Fluticasone (ICS) to prevent acute exacerbations.
Area under the curve for FEV1 (0 to 12 h) comparing salmeterol (LABA)–fluticasone (ICS) and Indacaterol (LABA)–Glycopyrronium (LAMA) (QVA149)

*p < 0.0001 for comparisons between QVA149 and SFC

For COPD receiving tiotropium plus salmeterol, the risk of moderate or severe exacerbations was similar among those who discontinued inhaled glucocorticoids or not. There was a greater decrease in lung function during glucocorticoid withdrawal.
BLOOD EOSINOPHILOS AS A PREDICTOR OF EXACERBATIONS RISK AFTER STEROIDS WITHDRAWAL

Increased risk of exacerbations during Steroid withdrawal if eosinophilia >300/uL

Increased rate ratio with ICS withdrawal

Watz et al. WISDOM  Lancet resp med 2016
Combined Assessment of COPD

<table>
<thead>
<tr>
<th>Risk (GOLD Classification of Airflow Limitation)</th>
<th>Symptom Score</th>
<th>Breathlessness Score</th>
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<tbody>
<tr>
<td>CAT &lt; 10</td>
<td>CAT ≥ 10</td>
<td></td>
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<tr>
<td>mMRC 0–1</td>
<td>mMRC ≥ 2</td>
<td></td>
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- (A) Risk ≥ 2 or ≥ 1 leading to hospital admission (not leading to hospital admission)
- (B) Risk 0
- (C) Risk 1
- (D) Risk 0

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Exacerbations per year

GOLD 4

GOLD 3

GOLD 2

GOLD 1

CAT < 10

mMRC 0-1

LAMA and LABA

or

LAMA and PDE4-inh

or

LABA and PDE4-inh

GOLD 4

ICS + LABA and LAMA

or

ICS + LABA and PDE4-inh

or

LAMA and LABA

or

LAMA and PDE4-inh.

GOLD 3

GOLD 2

GOLD 1

CAT ≥ 10

mMRC ≥ 2

LAMA and LABA

or

LAMA and PDE4-inh

or

LABA and PDE4-inh

or

SABA and SAMA

Pharmacologic Therapy of stable COPD

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Eosinophils >300/uL or Asthma COPD Overlap Syndrome

2 or more

≥ 1 leading to hospital admission

1 (not leading to hospital admission)
Additional drugs for COPD with frequent exacerbations:

- Roflumilast (PDE4 inhibitor)
- Azithromycin
- N-Acetyl cysteine
In June 2010, Roflumilast was approved in the EU for severe COPD associated with chronic bronchitis.

Martinez FJ, Calverley PMA, Goehring UM, et al. COPD 2010; poster 12.
Azithromycin maintenance treatment in patients with frequent exacerbations of chronic obstructive pulmonary disease (COLUMBUS): a randomised, double-blind, placebo-controlled trial


(500mg 3x/week)

OR: 0.58 (0.42-0.79; p<0.001)
In patients with chronic bronchitis, NAC should be administered at a dose of $\geq 1200$ mg per day to prevent exacerbations.
Relation between *Influenza vaccination* and hospitalisations in elderly persons with chronic lung diseases

NB: *Influenza vaccination* was associated also with fewer hospitalisations and fewer deaths

K.L. Nichol et al Ann Int Med 1999;130:397
Exercise to improve quality of life and decrease exacerbation rate

NB: decreased hospitalisation rate !!

Richard Casaburi et al
NEJM 2009:360;13
CONCLUSIONS

- **COPD exacerbations** lead to decline in lung function, enhanced morbidity and mortality (cardiovascular,...)
- Short course of **oral steroids** decrease the length of exacerbation and their recurrence.
- **Antibiotics** given for purulent secretions decrease the length of COPD exacerbations and their recurrence.
- **Long lasting anticholinergiques and Beta agonists** have a marked additive bronchodilator effect and reduce the rate of exacerbations.
- **Inhaled steroids should be restricted to Asthma COPD Overlap Syndrome (ACOS)** or to COPD with eosinophilic component (>300/uL)
- **Roflumilast** is efficient in reducing chronic bronchitis exacerbations.
- **Azithromycine** reduces the rate of COPD exacerbations.
- **Readaptation** increase quality of life and reduce COPD hospitalisation rate.
Thanks for your attention

Enjoy Lausanne!