Acute Exacerbations of COPD- Is the hospital necessary?

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Burden of COPD

- 10.3 million individuals with COPD
- 149,205 directly attributable deaths / year (2013)
- 507,077 hospitalizations/year (2013)
- $36 billion in attributable health expenditure-hospital admission (2010)

Definition

“An exacerbation of COPD is an acute event characterized by a worsening of the patient’s respiratory symptoms that is beyond normal day to day variations and leads to a change in medication”

GOLD guidelines 2016
Causes

• Infection
• Air pollutants, environmental
• Idiopathic
  - Pulmonary embolism
  - Ischemic heart disease
  - CHF
  - Aspiration
  - Pneumonia
Pathogenesis

• Acute inflammatory event superimposed on chronic inflammation associated with COPD, possibly leading to tissue destruction
  - Increase in inflammatory markers locally (EBx, sputum, BAL)
  - Increase in inflammatory markers systemically (serum fibrinogen, IL-6, CRP, procalcitonin)
  - Increased urinary excretion of desmosin
Acute Exacerbations of Chronic Obstructive Pulmonary Disease
Identification of Biologic Clusters and Their Biomarkers

- Observational study of 145 patients who had biomarkers measured at baseline and exacerbations followed over 1 year
- 86 patients experienced 182 AE events
- 4 distinct types of exacerbations:
  - Bacterial 37% (neutrophilic, sputum IL 1β)
  - Viral 10% (serum CXCL10)
  - Eosinophilic 17% (peripheral eosinophilia)
  - Pauciimmune 14%

Bafadhel M AJRCCM 2011; 184:662
Effect on Natural Course of COPD

Severe (and frequent) exacerbations increase risk of death 4 times compared to patients who do not have an exacerbation

Changes in Lung Function

• Frequent “exacerbators” (>3 /year) lose 40.1 ml/year compared to infrequent exacerbators’ 32.1 ml/year\(^1\)

• Single exacerbation may cause decline that may not return to baseline for weeks\(^2\)

\(^1\)Donaldson GC *Thorax* 2002
\(^2\)Seemungal TA *AJRCCM* 2000
2138 patients across severity spectrum followed for 3 years

History of AECOPD was the single best predictor

Frequent AE phenotype stable over 3 years

BODE score, lower health status, GERD, leukocytosis and lower FEV$_1$ associated with the phenotype

Phenotype present across COPD severity

Hurst JR et al NEJM 2010;363:1128-38
Group C
Less symptoms
High risk

Group D
More symptoms
High risk

Group A
Less symptoms
Low risk

Group B
More symptoms
Low risk

Increasing symptoms

Risk
Increasing risk

(GOLD Airflow Limitation, FEV1<50%)

Risk
Exacerbation history

≥ 2

0-1

CAT<10 or mMRC<2

CAT≥10 or mMRC≥2
Cardiovascular Risk During Acute COPD Exacerbation

- Prospective study of arterial stiffness (aPWV) and cardiac markers in patients with COPD
- Baseline, exacerbation and recovery measurements (n = 55)

Patel A AJRCCM 2013; 188:1091
Cardiovascular Risk During Acute COPD Exacerbation

Mean ± 1SE Aortic Pulse Wave Velocity (m/s)

- Stable State
- Exacerbation Day 3
- Day 7
- Day 14
- Day 35

Patel A AJRCCM 2013; 188:1091
Triaging Patients with COPD During an Exacerbation
Hospitalization if:

- Inadequate response to OP treatment
- Increase in dyspnea
- Inability to eat and sleep
- Worsening oxygenation and ventilation
- Mental status change
- Lack of home support, inability to care for self
- Unclear diagnosis
- Comorbidities that confer high risk

ATS/ERS Position Paper *ERJ* 2004;23:932
## Risk Factors for *In-hospital* Mortality

Prospective French multicenter study (113 centers) of 794 patients with AECOPD

<table>
<thead>
<tr>
<th>Points</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>&lt;70</td>
<td>≥ 70</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical signs of severity</td>
<td>None</td>
<td>1-2</td>
<td>≥ 3</td>
<td></td>
</tr>
<tr>
<td>Baseline mMRC</td>
<td>0-1</td>
<td>2-3</td>
<td>4-5</td>
<td></td>
</tr>
</tbody>
</table>

### Mortality

- 0% Score 0-1
- 5% Score 2-3
- 12% Score >4

### Clinical signs of severity

- Impaired neurological status
- Use of accessory muscles
- Cyanosis
- Lower extremity edema
- Asterixis

# Predicting Hospital Mortality in AECOPD: DECAF score

<table>
<thead>
<tr>
<th>DECAF Score</th>
<th>Description</th>
<th>Circle</th>
</tr>
</thead>
<tbody>
<tr>
<td>D</td>
<td>eMRCD 5a (Too breathless to leave the house unassisted but independent in washing and/or dressing)</td>
<td>1</td>
</tr>
<tr>
<td>E</td>
<td>eMRCD 5b (Too breathless to leave the house unassisted and requires help with washing and/or dressing)</td>
<td>2</td>
</tr>
<tr>
<td>C</td>
<td>Eosinopenia (eosinophils &lt;0.05x10^9/L)</td>
<td>1</td>
</tr>
<tr>
<td>A</td>
<td>Moderate or severe acidemia (pH &lt;7.3)</td>
<td>1</td>
</tr>
<tr>
<td>F</td>
<td>Atrial fibrillation (including history of paroxysmal atrial fibrillation)</td>
<td>1</td>
</tr>
</tbody>
</table>

**Total**

eMRCD, extended Medical Research Council dyspnea score.

Steer J et al *Thorax* 2012;67:970-6
Echevarria C et al *Thorax* 2016;71:133-140
Predicting Hospital Mortality in AECOPD: DECAF Score

Echevarria C et al Thorax 2016;71:133-140
Hospital at Home / Early Supported Discharge

HAH/ESD
HAH/ESD

- Management of a COPD patient, deemed appropriate for hospital admission, at home
- Patients recruited from the emergency room or after a short hospital stay
- Goals:
  - Cost reduction
  - Prevent nosocomial complications
  - Offer patients a choice
HAH/ESD Meta-Analysis

- 8 RCTs, published within the last 15 years
- Exclusion criteria:
  - Active comorbidity (acute MI, pulmonary embolism, GI bleeding etc.)
  - Acidemia (pH < 7.35)
  - Impaired consciousness
  - Social reasons e.g. homelessness
- Inclusion criteria
  - COPD exacerbation
  - Stringent spirometric criteria 3 out of 8 trials

HAH / ESD

- Recruitment within first 48 hours
- Intervention:
  - Home visits from respiratory nurses (physician supervision)
  - 1 study with both nurse and physician visit
  - Phone support
- Heterogeneity in protocols
  - Number of visits (2.6-14.1)
  - Number of phone calls
  - Physiotherapy
  - Occupational therapy
  - Patient and caregiver education
# HAH / ESD Meta-Analysis
## Readmission (7 studies)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>ESD / HAH Events</th>
<th>ESD / HAH Total</th>
<th>Usual care Events</th>
<th>Usual care Total</th>
<th>Weight</th>
<th>Risk Ratio M-H, fixed, 95% CI</th>
<th>Risk Ratio M-H, fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>2 month readmission</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cotton 2000</td>
<td>12</td>
<td>41</td>
<td>12</td>
<td>40</td>
<td>8.9%</td>
<td>0.98 [0.50, 1.91]</td>
<td></td>
</tr>
<tr>
<td>Nissen 2007</td>
<td>6</td>
<td>22</td>
<td>8</td>
<td>22</td>
<td>5.9%</td>
<td>0.75 [0.31, 1.80]</td>
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<tr>
<td>Skwarska 2000</td>
<td>39</td>
<td>130</td>
<td>21</td>
<td>61</td>
<td>20.4%</td>
<td>0.94 [0.61, 1.45]</td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>183</td>
<td>123</td>
<td></td>
<td></td>
<td>35.1%</td>
<td>0.92 [0.66, 1.29]</td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>57</td>
<td>41</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>3 month readmission</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Davies 2000</td>
<td>37</td>
<td>95</td>
<td>17</td>
<td>45</td>
<td>16.9%</td>
<td>1.03 [0.66, 1.62]</td>
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<tr>
<td>Ojoo 2002</td>
<td>11</td>
<td>29</td>
<td>12</td>
<td>27</td>
<td>9.1%</td>
<td>0.85 [0.46, 1.60]</td>
<td></td>
</tr>
<tr>
<td>Utens 2012</td>
<td>18</td>
<td>66</td>
<td>17</td>
<td>56</td>
<td>13.5%</td>
<td>0.90 [0.51, 1.57]</td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>190</td>
<td>128</td>
<td></td>
<td></td>
<td>39.4%</td>
<td>0.94 [0.69, 1.28]</td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>66</td>
<td>46</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>6 month readmission</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Davies 2008</td>
<td>20</td>
<td>41</td>
<td>34</td>
<td>39</td>
<td>25.5%</td>
<td>0.56 [0.40, 0.78]</td>
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</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>41</td>
<td>39</td>
<td></td>
<td></td>
<td>25.5%</td>
<td>0.56 [0.40, 0.78]</td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>20</td>
<td>36</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.84 [0.69, 1.01]</td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>143</td>
<td>121</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Favors ESD / HAH
Favors usual care
## HAH / ESD Meta-Analysis

**Mortality (7 studies)**

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
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<th>Usual care</th>
<th>Risk Ratio M-H, fixed, 95% CI</th>
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<tr>
<td><strong>2 month mortality</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cotton 2000</td>
<td>1 41</td>
<td>2 40</td>
<td>6.1% 0.49 [0.05, 5.17]</td>
<td></td>
</tr>
<tr>
<td>Nissen 2007</td>
<td>1 22</td>
<td>0 22</td>
<td>1.5% 3.00 [0.13, 69.87]</td>
<td></td>
</tr>
<tr>
<td>Skwarska 2000</td>
<td>4 122</td>
<td>7 62</td>
<td>28.0% 0.29 [0.09, 0.95]</td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>185</td>
<td>124</td>
<td>35.6% 0.44 [0.17, 1.12]</td>
<td></td>
</tr>
<tr>
<td><strong>Total events</strong></td>
<td>6</td>
<td>9</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>3 month mortality</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Davies 2000</td>
<td>9 95</td>
<td>4 45</td>
<td>16.4% 1.07 [0.35, 3.28]</td>
<td></td>
</tr>
<tr>
<td>Ojoo 2002</td>
<td>1 27</td>
<td>3 27</td>
<td>9.0% 0.33 [0.04, 3.01]</td>
<td></td>
</tr>
<tr>
<td>Utens 2012</td>
<td>1 66</td>
<td>1 56</td>
<td>3.3% 0.85 [0.05, 13.26]</td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>188</td>
<td>128</td>
<td>28.6% 0.81 [0.32, 2.03]</td>
<td></td>
</tr>
<tr>
<td><strong>Total events</strong></td>
<td>11</td>
<td>8</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>6 month mortality</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aimonino Ricauda 2008</td>
<td>9 50</td>
<td>12 51</td>
<td>35.8% 0.77 [0.35, 1.65]</td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>50</td>
<td>51</td>
<td>35.8% 0.76 [0.35, 1.65]</td>
<td></td>
</tr>
<tr>
<td><strong>Total events</strong></td>
<td>9</td>
<td>12</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>423</td>
<td>303</td>
<td>100.0% 0.66 [0.40, 1.09]</td>
<td></td>
</tr>
<tr>
<td><strong>Total events</strong></td>
<td>26</td>
<td>29</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Cost for acute episode is lower for Hospital at Home versus in-hospital care (4 studies)

However, only one study considered post acute care costs with no difference (community nursing and readmissions)
Caveats

- Only 25% of patients qualified for trials
- Inclusion criteria without objective risk stratification
- Time of recruitment variable (3/8 from ER)
- Ascertainment of outcome (readmissions, cost)
- None of the studies are from the USA
Prevention of Exacerbations
Pharmacotherapy of Stable COPD

• Short acting bronchodilators (SABA and SAMA)
• Long-acting bronchodilators (LABA and LAMA)
• Inhaled corticosteroids (ICS)
• Combined therapy (LABA+ICS)
• Dual therapy (LAMA+LABA)
• Triple therapy (LAMA+LABA+ICS)
• *Oral phosphodiesterase-4 inhibitor*
• *Macrolides*
Combined Therapy (LABA+ICS)

- TORCH (n=6112) and SUMMIT (n=16,485) trials
- Moderately severe symptomatic COPD
- Mortality reduction not realized
- Reduced exacerbations, reduced symptoms
- Reduced FEV$_1$ decline (8 ml/year) in the SUMMIT trial
- Pneumonia risk
- Cardiovascular events

Calverley et al. *NEJM* 2007;356:775-789
A 4-Year Trial of Tiotropium in Chronic Obstructive Pulmonary Disease

Double blind RCT of 5993 patients with COPD FEV$_1$ <70% (post bd)

Tiotropium versus placebo (no other anticholinergics) for 4 years

Primary endpoint, reduction in rate of FEV$_1$ decline, not realized

QOL improved

AECOPD rate was reduced (0.85 vs 0.73/patient year)
Triple Therapy - ICS = Dual Therapy
**Triple Therapy - Dual Therapy = ICS**

Do we Need ICS?

<table>
<thead>
<tr>
<th>Pros</th>
<th>Cons</th>
</tr>
</thead>
</table>
| • Potential impact on exacerbations       | • Skin thinning and easy bruising
| • Biological plausibility for certain phenotypes | Guillot B Expert Opin Drug Saf 2002; 1: 325–29       |
|   - CS reduce airway inflammation        | • Oral thrush, and hoarseness
|   - Upregulate beta receptors            | Sin DD JAMA 2003; 290: 2301–12.                       |
|   - Mild improvement in FEV$_1$ (initial sustained) | • Increased risk of pneumonia
|                                           | Calverley PM N Engl J Med 2007; 356: 775–89           |
|                                           | • Osteoporosis
|                                           | • Early onset diabetes                                |
|                                           | • Cataracts                                           |
|                                           | Cumming RG N Engl J Med 1997;337: 8–14                 |
|                                           | • Cost                                                |
|                                           | • No effect on FEV$_1$ decline                        |
Withdrawal of Inhaled Glucocorticoids and Exacerbations of COPD

- 2485 patients with severe COPD and history of ≥ 1 exacerbation
- 12-month, double-blind, noninferiority design
- All received triple therapy (Tio 18 μg QD+salmeterol 50 μg BID and fluticasone 500 μg BID) during a 6-week run-in
- Randomized to continue triple therapy or withdrawal of fluticasone (gradual over 3 months)
- Primary end point: time to first COPD exacerbation
- Spirometry, quality of life and dyspnea

Withdrawal of Inhaled Glucocorticoids and Exacerbations of COPD

Moderate or Severe COPD Exacerbation

Hazard ratio, 1.06 (95% CI, 0.94-1.19) 
P=0.35 by Wald’s chi-square test

Hazard Ratio (95% CI)

Noninferiority margin

0.8 0.9 1.0 1.1 1.2 1.3 1.4 1.5

IGC withdrawal better

IGC continuation better

IGC withdrawal

IGC continuation

Estimated probability

0.0 0.2 0.4 0.6 0.8 1.0

Weeks to event

0 6 12 18 24 30 36 42 48 54

Withdrawal of Inhaled Glucocorticoids and Exacerbations of COPD

- Nonsignificant increase in severe exacerbations after withdrawal
- Reduced FEV₁ and QoL (albeit small)

Hazard ratio, 1.20 (95% CI, 0.98-1.48)
P=0.08 by Wald’s chi-square test

It’s Dual Therapy: Case Closed?

- WISDOM says: Dual therapy is not unacceptably worse than triple therapy
- Unacceptably worse: increase in exacerbations by more than 20%
- Severe exacerbations, QoL, lung function
Combined Versus Dual Bronchodilator Therapy: FLAME Trial

- 52-week randomized, double-blind, double-dummy non-inferiority trial
- Moderate to severe COPD (FEV₁ 25-59%) with history of 1 exacerbation during the past year
- 1680 patients indacaterol+glycopyronium, 1682 salmeterol+fluticasone
- Well matched for demographics, smoking status, lung function impairment and use of inhaled corticosteroids
- Primary endpoint annual rate and time to first exacerbation

Wedzicha JA et al NEJM 2016; 374:2222-34
Combined Versus Dual Bronchodilator Therapy: FLAME Trial

Hazard ratio, 0.84 (95% CI, 0.78-0.91)  
P<0.001

Hazard ratio, 0.78 (95% CI, 0.70-0.86)  
P<0.001

Hazard ratio, 0.81 (95% CI, 0.66-1.00)  
P=0.046

Wedzicha JA et al NEJM 2016; 374:2222-34
Combined Versus Dual Bronchodilator Therapy: FLAME Trial

Per-protocol population

Modified intention-to-treat population

Superiority margin

Noninferiority margin

Indacaterol-Glycopyronium Better

Salmeterol-Fluticasone Better

0.83 0.89 0.96

0.82 0.88 0.94

P=0.003

P<0.001

Wedzicha JA et al NEJM 2016; 374:2222-34
Current smokers, patients with severe lung function impairment, patients with previous LAMA or LABA use benefited more.

Patients with eosinophilia (>2%) had lower exacerbation rate with LAMA+LABA.

Wedzicha JA et al. NEJM 2016; 374:2222-34
Prevention of Exacerbations
Pharmacotherapy: Roflumilast

- PDE-4 inhibitor with anti-inflammatory action without acute bronchodilator properties
- Severe COPD, chronic bronchitis and history of exacerbations
• Double blind multicenter RCT, 1 year follow-up

• 1945 patients with severe COPD, chronic bronchitis, history of ≥ 2 exacerbations

• All on LABA/ICS and 70% on LAMA

• Randomized to LABA/ICS + roflumilast vs LABA/ICS + placebo

• LAMA continued if already using

Martinez FJ et al Lancet 2015;385:857-866
Results

Number at risk
Placebo (432)
Roflumilast (380)
Placebo (369)
Roflumilast (310)

Rate ratio (95% CI)
0.858 (0.753-1.002)
0.806 (0.688-0.943)

2-sided p value
0.0529
0.0070

Mean rate of chronic obstructive pulmonary disease exacerbations per patient per year

Intention to treat
Per protocol

0.927
0.805
0.921
0.742
Prevention of Exacerbations
Pharmacotherapy: Roflumilast

- Benefit:Harm ratio may not be favorable for most patients with COPD given the drug side effects

Yu T et al Thorax 2013;epub December 17, 2013
Prevention of Exacerbations
Pharmacotherapy: Macrolides

- Macrolide antibiotics have anti-inflammatory and immunomodulatory activity
- Multicenter RCT of daily azithromycin therapy showed reduced exacerbation rate without change in hospitalizations and increased hearing loss

Albert RK et al. *NEJM* 2011;365:689
Randomized, double-blind, placebo-controlled, single center study

92 patients with COPD and ≥3 exacerbations during the past year

Bronchiectasis excluded with CT chest

Azithromycin 500 mg thrice weekly versus placebo

ICS (92%), LABA (93%), LAMA (80%)

Exacerbation rate 1.94/patient/year in the azithromycin group vs 3.22 (adjusted RR 0.58, 0.42-0.79; p=0.001.

Prevention of Exacerbations

- Pharmacotherapy
  - LAMA
  - LAMA+LABA
  - LABA-ICS
  - Phosphodiesterase inhibitors
  - LABA
  - ICS*
  - Macrolides
  - Mucolytics

- Vaccinations

- Smoking cessation

- Pulmonary rehabilitation

- Lung volume reduction surgery
Summary

• Exacerbations are associated with lower QOL, faster decline in lung function and mortality
• Infections are the most common etiology for exacerbations
• Fatalities can occur due to exacerbation mimics
• Exacerbation phenotypes may define therapy in the near future
• Hospital at home is feasible and safe in selected patients but requires significant planning and commitment of resources. Cost effectiveness is unknown
• LAMA, LAMA / LABA or LABA / ICS are preferred treatments which reduce rate of exacerbations
• Low dose-long term macrolide therapy or roflumilast may be considered as part of a preventative regimen
Cleveland Clinic
Every life deserves world class care.