COPD Exacerbations: What should you know?

Alan Kaplan MD CCFP(EM) FCFP
Chairperson,
Family Physician Airways Group of Canada
Respiratory Section of CFPC
Case

- 75 year old man comes in to ER
- 72 hours of increased cough, sputum, coloured sputum and overall deterioration
- Hx of COPD taking Spiriva and Advair
- Too SOB to say more than a few words
- ? Cyanotic

- How serious is this condition?
- What do you want to do, treatments, tests?
- Who can go home?
- How can we prevent this happening for this poor man?
DISCLOSURE

Dr. Alan G. Kaplan
Chair, Family Physician Airways Group of Canada

Perceive no conflict of interest with giving this presentation, but present the following companies that I have worked with or consulted for:
Astra Zeneca, Bayer, Boehringer Ingeleheim, Graceway, GSK, JOI, Merck Frosst, Novartis, Nycomed, Pfizer, Purdue, and Talecris.

In addition, I am on Health Canada committee for Section of Allergy and Respiratory Therapeutics and Public Health Agency of Canada Section of Respiratory Surveillance
The Burden of COPD
Lifetime risk of COPD = 27.6%
Cigarette Related Diseases
Leading Causes of Death Worldwide 2010

1. Myocardial Infarction
2. Cancer
3. Cerebrovascular Diseases
4. COPD

Leading Causes of Death in CANADA
COPD Is The Only Major Cause Of Death That Has Increased Significantly

Percentage change in age-adjusted death rates in USA, from 1965 to 1998

CVD = cerebrovascular disease

www.goldcopd.com
COPD - #1 Cause for Hospital Admissions Among Chronic Illness

will kill 10,000 Canadians this year and every year after\textsuperscript{1} will surpass stroke to become the 3\textsuperscript{rd} leading cause of death by 2020\textsuperscript{2}

\textsuperscript{1} Public Health Agency of Canada. Life and Breath: Respiratory Diseases in Canada, 2007.
\textsuperscript{2} WHO
COPD has pulmonary and systemic components

Chronic disease

- progressive nature
  - lung function
  - symptoms
  - comorbidities

Exacerbations

- typically 1 - 3 per year
- frequency proportional to COPD severity
- the frequent exacerbator
- chronic decline resulting in poorer prognosis
  - ↓ HRQL
  - ↑ hospitalizations
  - ↑ mortality

Canadian Physicians’ Perceptions of the Long-Term Impact of Serious Exacerbations

- **Asthma attack**
  - No long-term impact: 25%
  - A slight long-term impact: 11%
  - A moderate long-term impact: 27%
  - A major long-term impact: 48%
  - A very major long-term impact: 9%

- **Pneumonia**
  - No long-term impact: 15%
  - A slight long-term impact: 4%
  - A moderate long-term impact: 25%
  - A major long-term impact: 19%
  - A very major long-term impact: 37%

- **COPD exacerbation**
  - No long-term impact: 13%
  - A slight long-term impact: 29%
  - A moderate long-term impact: 48%
  - A major long-term impact: 9%
  - A very major long-term impact: 1%

- **Myocardial infarction**
  - No long-term impact: 8%
  - A slight long-term impact: 45%
  - A moderate long-term impact: 28%
  - A major long-term impact: 19%

- **Stroke**
  - No long-term impact: 11%
  - A slight long-term impact: 30%
  - A moderate long-term impact: 58%
  - A major long-term impact: 1%
  - A very major long-term impact: 1%
COPD Exacerbations: Those at Greater Risk and the Impact
CTS Definition of Acute Exacerbation of COPD

Sustained (≥48 h) worsening of dyspnea, cough or sputum production

• An increase in the use of maintenance medications
  and/or
• Supplementation with additional medications

Factors Associated With Increased Risk for Exacerbations

- Increased age
- Severity of airway obstruction (FEV\textsubscript{1} impairment)
- Chronic bronchial mucous hypersecretion
- Longer duration of COPD
- Productive cough and wheeze
- Elevated cough and sputum
- Antibiotic or systemic corticosteroid use in the past year
- Prior use of medications for COPD
- Bacterial colonisation
- Comorbid conditions (e.g., cardiovascular disease)
- Poor health-related quality of life

Epidemiology of Exacerbations: Frequency Increases With Declining FEV₁

Cough and Sputum: One of the Susceptible Phenotypes for COPD Exacerbators

ASSOCIATION OF DISEASE SEVERITY WITH THE FREQUENCY AND SEVERITY OF EXACERBATIONS DURING THE FIRST YEAR OF FOLLOW-UP IN PATIENTS WITH COPD

Association of Disease Severity with the Frequency and Severity of Exacerbations during the First Year of Follow-up in Patients with Chronic Obstructive Pulmonary Disease

Stability of the Frequent-Exacerbation Phenotype in the 1679 Patients with Chronic Obstructive Pulmonary Disease Who Completed the Study

URI and AECOPD. Cause or effect?

- 150 patients with COPD
- completed diary cards recording peak expiratory flow, and respiratory and coryzal symptoms for a median 1,047 days.
- Annual cold and exacerbation incidence rates (cold and exacerbation frequency) were calculated, and the relationships between these variables were investigated.
- This analysis is based on 1,005 colds and 1,493 exacerbations.

URI and AECOPD. Cause or effect

- Exacerbation frequency in chronic obstructive pulmonary disease is associated with an increased frequency of acquiring the common cold, rather than an increased propensity to exacerbation once a cold has been acquired.

Exacerbations are more frequent and severe in winter

Frequency reporting by season, TORCH data¹

Symptom severity²

The Christmas Peak

![Bar graph showing study week versus emergency department visits for chronic obstructive pulmonary disease among the population of Hamilton, Ontario, from December 1, 2006, to April 30, 2007. Absolute number of emergency department visits for chronic obstructive pulmonary disease initiated by residents of Hamilton during the first 17 weeks of the study period (data for April 2007 not available). Week 5 represents December 29, 2006, to January 4, 2007.]

What does an exacerbation mean to a patient?

Decline in lung function

Greater anxiety

Social withdrawal

Increased risk of mortality

Increased risk of hospitalisation (I.e. breathlessness)

Worsening quality of life

More & more severe exacerbations

Increased risk of mortality

Exacerbation Frequency Increases Mortality Risk and Lung Function Decline

Group A  Patients with no acute exacerbations
Group B  Patients with 1–2 acute exacerbations requiring hospital management
Group C  Patients with >3 acute exacerbations

Symptom scores during an Exacerbation

- Breathing
- Cough
- Chest tightn.
- Sleep
**Activity Decreases During Exacerbations**

- 17 patients
- Hospitalized for exacerbation
- Activity monitor

Pitta F et al., *Chest* 2006; 129:536-544.
Days -7 to -1 p < 0.05

TIME COURSE OF AN EXACERBATION

Seemungal et al. Am J Respir Crit Care Med 2000
SGRQ vs AECOPD Recurrence

Methodology

➢ A two part online self completion survey
  ➢ COPD patients – 150 interviews per market (except Denmark and Turkey – 100 patients)
  ➢ Physicians treating COPD patients – 100 interviews per market

➢ Fourteen markets in total

<table>
<thead>
<tr>
<th>Brazil</th>
<th>Canada</th>
<th>Denmark</th>
</tr>
</thead>
<tbody>
<tr>
<td>France</td>
<td>Germany</td>
<td>Italy</td>
</tr>
<tr>
<td>Netherlands</td>
<td>Poland</td>
<td>South Korea</td>
</tr>
<tr>
<td>Spain</td>
<td>Turkey</td>
<td>UK</td>
</tr>
<tr>
<td>China</td>
<td>Australia</td>
<td></td>
</tr>
</tbody>
</table>

➢ Questionnaires developed by an international steering committee comprised of respiratory specialists in conjunction with ICM Research and with the support of Nycomed and FD Santé

➢ To qualify for interview all physicians had to be either…
  ➢ GPs that treat a minimum of 10 patient a month suffering from COPD
  ➢ Respiratory specialists that treat a minimum of 20 patients a month suffering from COPD

Unpublished data conducted by Nycomed
Average number of ‘attacks’ in last year

Around seven in ten of those interviewed had experienced an attack in the past twelve months.

EX11 In the past 12 months, how many times have you experienced one of these attacks?
Base: All respondents (1906)
Assessing Disability in COPD – MRC Dyspnea Scale

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Breathless with strenuous exercise</td>
</tr>
<tr>
<td>2</td>
<td>Short of breath when hurrying on the level or walking up a slight hill</td>
</tr>
<tr>
<td>3</td>
<td>Walks slower than people of the same age on the level or stops for breath while walking at own pace on the level</td>
</tr>
<tr>
<td>4</td>
<td>Stops for breath after walking 100 yards</td>
</tr>
<tr>
<td>5</td>
<td>Too breathless to leave the house or breathless when dressing</td>
</tr>
</tbody>
</table>

Figure 3. Medical Research Council (MRC) dyspnea scale. From: Fletcher CM, Elmes PC, Wood CH. The significance of respiratory symptoms and diagnosis of chronic bronchitis in a working population. Br Med J 1959; 1:257-266.
Average number of ‘attacks’ in last year
– by MRC classification

Those with MRC 3,4&5 COPD tend to experience a greater number of exacerbations

EX11 In the past 12 months, how many times have you experienced one of these attacks?
Base: All respondents (1906)
Exacerbations have a Major Impact on QoL

<table>
<thead>
<tr>
<th>TOTAL AFFECTED:</th>
<th>60%</th>
<th>95%</th>
<th>89%</th>
<th>58%</th>
<th>92%</th>
<th>82%</th>
<th>56%</th>
<th>60%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not applicable</td>
<td>30%</td>
<td>16%</td>
<td>21%</td>
<td>36%</td>
<td>12%</td>
<td>40%</td>
<td>39%</td>
<td>23%</td>
</tr>
<tr>
<td>Cannot do at all</td>
<td>18%</td>
<td>54%</td>
<td>24%</td>
<td>24%</td>
<td>40%</td>
<td>39%</td>
<td>41%</td>
<td>33%</td>
</tr>
<tr>
<td>Significantly affected</td>
<td>19%</td>
<td>19%</td>
<td>44%</td>
<td>22%</td>
<td>40%</td>
<td>39%</td>
<td>41%</td>
<td>38%</td>
</tr>
<tr>
<td>Somewhat affected</td>
<td>23%</td>
<td>25%</td>
<td>8%</td>
<td>7%</td>
<td>6%</td>
<td>15%</td>
<td>41%</td>
<td>38%</td>
</tr>
<tr>
<td>Not at all affected</td>
<td>11%</td>
<td>2%</td>
<td>2%</td>
<td>1%</td>
<td>3%</td>
<td>1%</td>
<td>4%</td>
<td>4%</td>
</tr>
</tbody>
</table>

Sex life
- Climbing stairs
- Housework
- Work
- Walking
- Sleeping
- Speech
- Getting dressed

Not applicable
- Cannot do at all
- Significantly affected
- Somewhat affected
- Not at all affected
Impact of exacerbations compared to living with COPD: walking

Ability to walk is significantly impacted by exacerbations

EX13 From the following list can you indicate to what extent your ability to undertake or participate in these activities or pastimes are directly affected or restricted when you are experiencing one of these attacks?
Base: All respondents who have ever experienced a worsening of at least one symptom of their Chronic Bronchitis/ Emphysema/ COPD (1460)
Impact of exacerbations compared to living with COPD: sex life

Exacerbations affect patients sex lives

EX13 From the following list can you indicate to what extent your ability to undertake or participate in these activities or pastimes are directly affected or restricted when you are experiencing one of these attacks?
Base: All respondents who have ever experienced a worsening of at least one symptom of their Chronic Bronchitis/ Emphysema/ COPD (1460)
Pulmonary Function May Recover Slowly After an Exacerbation

More Rapid Decline in FEV$_1$ With Higher Exacerbation Frequency

OUTCOME OF COPD EXACERBATIONS

- In ICU patients: Hospital mortality - 20%-24% (1 year)
- In hospitalized patients: Hospital mortality - 2.5%-10% (5 days)
- In ER patients: Relapse (repeat ER visit) - 22%-32% (14 days)
- In outpatients: Treatment failure rate - 13%-33% (14 days)

Exacerbation Frequency and Severity Both Increase Mortality Risk

Group A patients with no acute exacerbations
Group B patients with 1–2 acute exacerbations requiring hospital management
Group C patients with ≥3 acute exacerbations

Group (1) no acute exacerbations
Group (2) acute exacerbations requiring emergency service visits without admission
Group (3) patients with acute exacerbations requiring one hospital admission
Group (4) patients with acute exacerbations requiring readmissions

Outcomes After Hospitalized AECOPD

At 6 months
- 446 admitted 754 times
- 26% alive and good to excellent quality of life

Survival time related to:
- severity of COPD
- BMI
- prior functional status
- Pa02/FIO2
- CHF
- serum albumin
- cor pulmonale

Effect of COPD on Work

Respir Med 2003;97 (suppl C):S1-104
Other non-respiratory effects of AECOPD

- Psychologic
- Physical
Feelings Associated with Exacerbations & their Impact

Kessler R et al. Chest 2006; 130:133-142
“Exacerbations of COPD”

Cardiovascular mechanisms of death in severe COPD exacerbation: time to think and act beyond guidelines

Leonardo M Fabbri,¹ Bianca Beghé,¹ Alvar Agusti²

Thorax 2011;66:745-6

‘exacerbations of COPD’

- v -

‘exacerbations of respiratory symptoms in patients with COPD’
## Systemic Effects of Exacerbations

<table>
<thead>
<tr>
<th></th>
<th>Before exacerbation</th>
<th>After exacerbation</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>IR*</td>
<td>N</td>
</tr>
<tr>
<td>Total</td>
<td>58</td>
<td>20.2</td>
<td>181</td>
</tr>
<tr>
<td>Cardiac failure</td>
<td>2</td>
<td>0.69</td>
<td>28</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>5</td>
<td>1.73</td>
<td>23</td>
</tr>
<tr>
<td>Atrial fibrillation/flutter</td>
<td>1</td>
<td>0.35</td>
<td>17</td>
</tr>
<tr>
<td>MI</td>
<td>1</td>
<td>0.35</td>
<td>13</td>
</tr>
<tr>
<td>Angina</td>
<td>4</td>
<td>1.39</td>
<td>11</td>
</tr>
<tr>
<td>Stroke</td>
<td>2</td>
<td>0.69</td>
<td>9</td>
</tr>
<tr>
<td>Non-ventricular tachycardia (inc. SVT)</td>
<td>0</td>
<td>0</td>
<td>7</td>
</tr>
</tbody>
</table>

* IR per 100 patient-years.

IRs and RRs 30 days before and after the first exacerbation for the most common non-respiratory SAEs by prespecified adverse event category

Halpin et al Lung 2011; 189(4):261-8
Pathophysiology of Systemic Effects of Exacerbations

During Exacerbations:

• Troponin T & NT-BNP are elevated and are associated with increased mortality
  • Renal endothelin-1 production is increased
  • Circulating fibrinogen levels are increased
  • Circulating platelet/monocyte aggregates are increased
  • Markers of oxidative stress are increased
Let’s call an AECOPD a....

LUNG ATTACK!!
Typical Patient Reaction to an Exacerbation
Global vs. Canada

- **57% Take action**
- **39% Wait and see**
- **5% Do nothing**

**TOTAL**

- **57% Take action**
- **39% Wait and see**
- **5% Do nothing**

**CANADA**

- **48% Take action**
- **45% Wait and see**
- **8% Do nothing**
Burden of Unreported Exacerbations

N=491

95% CI = 0.09-9.13

95% CI = -4.05-6.48

Patients under-report exacerbations

- Patients reported only 50–60% of exacerbations

GOLD: Goals for COPD Treatment

- Disease prevention is the ultimate goal of COPD treatment
- Once COPD has been diagnosed, effective management should be aimed at the following goals:
  - Relieve symptoms
  - Improve exercise tolerance
  - Improve health status
  - Prevent and treat exacerbations
  - Prevent disease progression
  - Prevent and treat complications
  - Reduce mortality

Goal of COPD Management

Overall COPD Control

Achieving
Current Control defined by
- Symptoms
- Reliever use
- Activity
- Lung function

Reducing
Future Risk defined by
- Exacerbations
- Mortality
- Progression of the disease
- Medication adverse effects

GOLD 2011 www.goldcopd.org
Potential Causes of Exacerbation
Potential Causes of Exacerbations

- Bacterial infection
- Viral infection
- Pollution:
  - Nitrogen dioxide
  - Particulates
  - Sulphur dioxide
  - Ozone
- Cold weather
- Interruption of regular treatment
- Other diseases: CHF, PE, Pneumonia, GERD

Relationship Between FEV$_1$ and Aetiology of Exacerbations

![Graph showing the relationship between FEV$_1$ and aetiology of exacerbations.](image-url)

Pathophysiology
COPD is a Disease Characterized by Inflammation

Numbers of Inflammatory Cells and Mediators Increase as COPD progresses

<table>
<thead>
<tr>
<th>Cell Type</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutrophils</td>
<td>67</td>
<td>55</td>
<td>84</td>
<td>100</td>
</tr>
<tr>
<td>Macrophages</td>
<td>54</td>
<td>66</td>
<td>73</td>
<td>92</td>
</tr>
<tr>
<td>Eosinophils</td>
<td>25</td>
<td>33</td>
<td>29</td>
<td>32</td>
</tr>
<tr>
<td>CD4⁺</td>
<td>63</td>
<td>87</td>
<td>77</td>
<td>94</td>
</tr>
<tr>
<td>CD8⁺</td>
<td>85</td>
<td>80</td>
<td>88</td>
<td>98</td>
</tr>
<tr>
<td>B cells</td>
<td>7</td>
<td>8</td>
<td>45</td>
<td>37</td>
</tr>
</tbody>
</table>

BUT airway inflammation is present in all stages of COPD

Inflammation in Asthma and COPD

ASTHMA

Allergen/Sensitizing Agent

Asthmatic airway inflammation
- CD4+ T-lymphocytes
- Eosinophils
- Macrophages
- Mast cells

Mostly irreversible

COPD

Cigarette Smoke/Noxious Agent

COPD airway inflammation
- CD8+ T-lymphocytes
- Neutrophils
- Macrophages

Mostly reversible

Mostly reversible
AIRFLOW LIMITATION

Bronchial Neutrophils Are Increased During Some Exacerbations

* P<0.01 versus stable disease

Bronchial Eosinophils Are Increased During Exacerbations

* $P<0.001$ versus stable disease

Aetiology of Exacerbations for Different COPD Stages

- $S$ pneumoniae and Gram positive cocci
- $H$ influenzae/M catarrhalis
- Enterobacteriaceae/Pseudomonas spp

$P=0.016$ for differences in distributions

TREATMENT
Meta-analysis of Efficacy: Systemic Corticosteroids and Risk for Treatment Failure

Favors Steroid  Favors Placebo

- Bullard et al, 1996
- Thompson et al, 1996
- Davies et al, 1999
- Niewoehner et al, 1999
- Maltais et al, 2002
- Aaron et al, 2003

Pooled summary (RR, 0.54; 95% CI, 0.41-0.71)

Relative Risk (95% Confidence Interval)

Reproduced with permission of Chest, from “Contemporary Management of Acute Exacerbations of COPD”, Quon BS et al, Vol 133, Copyright © 2008; permission conveyed through Copyright Clearance Center, Inc.
Oral Corticosteroids: Effect on FEV\textsubscript{1} in Patients With Exacerbations

Postbronchodilator FEV\textsubscript{1} (% predicted)

- Baseline: 25.4
- Post-Treatment: 32.2

* $P<0.0001$ versus baseline

Oral Corticosteroids for Treatment of Exacerbations

Rate of Treatment Failure (%)

$P=0.04$ for combined glucocorticoid groups versus placebo at 4 and 8 weeks

Patients at risk, $n$

- Glucocorticoids, 8 wk: 80, 61, 50, 21
- Glucocorticoids, 2 wk: 80, 59, 46, 20
- Placebo: 111, 74, 58, 39

# Suggested Antimicrobial Therapy

<table>
<thead>
<tr>
<th>Group</th>
<th>Probable Pathogens</th>
<th>First Choice</th>
<th>Alternatives for Treatment Failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>H. influenzae, M. catarrhalis, S. pneumoniae</td>
<td>2nd generation macrolide, 2nd or 3rd generation cephalosporin, amoxicillin, doxycycline, trimethoprim-sulfamethoxazole</td>
<td>Fluoroquinolone, β-lact/β-lactamase inhibitor</td>
</tr>
<tr>
<td>II</td>
<td>As in group I, plus: Klebsiella spp. and other gram-negative bacteria</td>
<td>Fluoroquinolone, β-lact/β-lactamase inhibitor</td>
<td>May require parenteral therapy, Consider referral to a specialist or hospital.</td>
</tr>
<tr>
<td>III</td>
<td>As in group II, plus: P. Aeruginosa and multi-resistant Enterobacteriaceae</td>
<td>Ambulatory - tailor treatment to airway pathogen; P. Aeruginosa common (ciprofloxacin); Hospitalized - parenteral therapy usually required</td>
<td></td>
</tr>
</tbody>
</table>

# Meta-analysis of Efficacy: Antibiotic Therapy and Risk for Treatment Failure

## Relative Risk (95% Confidence Interval)

<table>
<thead>
<tr>
<th>Study</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pooled summary</td>
<td>(RR, 0.54; 95% CI, 0.32-0.92)</td>
</tr>
<tr>
<td>Elmes et al, 1965</td>
<td></td>
</tr>
<tr>
<td>Pines et al, 1968</td>
<td></td>
</tr>
<tr>
<td>Anthonisen et al, 1987</td>
<td></td>
</tr>
<tr>
<td>Jorgensen et al, 1992</td>
<td></td>
</tr>
<tr>
<td>Nouira et al, 2001</td>
<td></td>
</tr>
</tbody>
</table>

---

Reproduced with permission of Chest, from “Contemporary Management of Acute Exacerbations of COPD”, Quon BS et al, Vol 133, Copyright © 2008; permission conveyed through Copyright Clearance Center, Inc.
Antibiotic Treatment Decreases Mortality in COPD Patients Mechanically Ventilated for Exacerbation

* $P=0.01$ versus placebo

Noninvasive Mechanical Ventilation (NIV)

Selection Criteria

- Moderate to severe dyspnoea with use of accessory muscles
- Moderate to severe acidosis (pH ≤7.35) and/or hypercapnia (PaCO₂ >6.0 kPa, 45 mm Hg)
- Respiratory frequency >25 breaths per minute

Contraindications

- Respiratory arrest
- Cardiovascular instability (hypotension, arrhythmias, myocardial infarction)
- Change in mental status; uncooperative patient
- High aspiration risk
- Viscous or copious secretions
- Recent facial or gastroesophageal surgery
- Craniofacial trauma
- Fixed nasopharyngeal abnormalities
- Burns
- Extreme obesity

Meta-analysis of Efficacy: NIV

Bolt et al, 1993
Desinkpoulou et al, 1993
Servillo et al, 1994
Brochard et al, 1995
Kramer et al, 1995
Angus et al, 1996
Cellical et al, 1998
Plant et al, 2000
Olkensoy et al, 2002
CRC et al, 2005
Dharnja et al, 2005
Keenan et al, 2005
Pooled summary
(RR.036: 96% CL 0.26-0.47)

Risk for Intubation

Favors NPPV

Favors Standard Therapy

Relative Risk (95% Confidence Interval)

0.01 0.1 1 10 100

Favors NPPV

Favors Standard Therapy

Relative Risk (95% Confidence Interval)

0.01 0.1 1 10 100

Reproduced with permission of Chest, from "Contemporary Management of Acute Exacerbations of COPD", Quon BS et al, Vol 133, Copyright © 2008; permission conveyed through Copyright Clearance Center, Inc.
Oxygen

Hypoxia during an acute episode can lead to pulmonary vasoconstriction, which can result in right heart strain, cor pulmonale, myocardial ischemia and low cardiac output. Efforts should be made to keep the arterial oxygen level above 60 mmHg. Maintain oxygen saturation between 90% to 92% to prevent the blunting of the respiratory drive in patients with underlying hypercapnia.1

Preventing COPD Exacerbations: Current Therapies and New Options
Influenza Vaccination: Risk for Any Exacerbation

- Evaluation of results from randomised clinical trials indicates that inactivated influenza vaccine reduces exacerbations in COPD patients.
- The magnitude of this benefit is similar to that seen in large observational studies, and was due to a reduction in exacerbations occurring three or more weeks after vaccination, and due to influenza.
- There is a mild increase in transient local adverse effects with vaccination, but no evidence of an increase in early exacerbations.

Pneumococcal Vaccination

- **Log rank** = 6.68
- **P** = 0.0097
- **Vaccinated** = 91
- **Control** = 116

- **Log rank** = 3.85
- **P** = 0.0498 (NS)
- **Vaccinated** = 132
- **Control** = 114

## Pulmonary Rehabilitation

<table>
<thead>
<tr>
<th>Study (in rehabilitation/Length of usual care group/follow-up)</th>
<th>Risk ratio (95% CI)</th>
<th>Weight in %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Behnke (14/12β months)</td>
<td>0.29 (0.10 to 0.82)</td>
<td>37%</td>
</tr>
<tr>
<td>Man (20/21) 3 months</td>
<td>0.17 (0.04 to 0.69)</td>
<td>44%</td>
</tr>
<tr>
<td>Murphy (13/13β months)</td>
<td>0.40 (0.09 to 1.70)</td>
<td>19%</td>
</tr>
<tr>
<td>Overall (47/46)</td>
<td>0.26 (0.12 to 0.54)</td>
<td></td>
</tr>
<tr>
<td>Chi-Squared 0.70, p=0.71</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Favors rehabilitation: Risk of unplanned hospital admission: Favors usual care

Optimal Pharmacotherapy

Increasing Disability and Lung Function Impairment

Mild

Moderate

Severe

Infrequent AECOPD (< 1/year)

Frequent AECOPD (≥ 1/year)

SABD prn

LAAC or LABA+ SABA prn

LAAC + ICS/LABA + SABA prn

LAAC prn

persistent dyspnea

LAAC + LABA + SABA prn

LAAC + ICS/LABA + SABA prn

persistent dyspnea

LAAC + ICS/LABA + SABA prn +/− Theophylline

POET-COPD®: Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Tiotropium (N=3707)</th>
<th>Salmeterol (N=3669)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male, %</td>
<td>74.4</td>
<td>74.9</td>
</tr>
<tr>
<td>Age, years*</td>
<td>62.9 (9.0)</td>
<td>62.8 (9.0)</td>
</tr>
<tr>
<td>Smoking status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current smoker, %</td>
<td>48.0</td>
<td>48.3</td>
</tr>
<tr>
<td>Smoking history, pack-years*</td>
<td>38.8 (20.0)</td>
<td>37.8 (19.2)</td>
</tr>
<tr>
<td>Duration of COPD, years*†</td>
<td>8.0 (6.7)</td>
<td>7.9 (6.5)</td>
</tr>
<tr>
<td>GOLD stage, %†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>47.8</td>
<td>49.6</td>
</tr>
<tr>
<td>III</td>
<td>43.1</td>
<td>42.1</td>
</tr>
<tr>
<td>IV</td>
<td>8.9</td>
<td>7.9</td>
</tr>
</tbody>
</table>

*Mean (standard deviation).
†Data on duration of COPD missing for 15 and 5 patients in tiotropium and salmeterol groups, respectively.
‡23 patients had GOLD stage I disease (tiotropium 0.2%; salmeterol 0.4%).
GOLD=Global Initiative for Chronic Obstructive Lung Disease.

Tiotropium Significantly Delayed Time to First Exacerbation

![Graph showing the probability of COPD exacerbation over time for Tiotropium and Salmeterol.](image

- **Hazard ratio:** 0.83* (95% CI, 0.77, 0.90)
- **P-value:** <0.001 (log-rank test)

* Cox regression adjusted for (pooled) centre and treatment.

**Risk difference:** 17%

Tiotropium Significantly Delayed Time to First Severe Exacerbation

Hazard ratio = 0.72* (95% CI, 0.61, 0.85)  
*P<0.001 (log-rank test)

*Cox regression adjusted for (pooled) centre and treatment.

Hazard ratio = 0.86, (95% CI = 0.81, 0.91) 
\( p < 0.001 \) (log-rank test)

Months

Tiotropium

Control

0.85/yr

0.73/yr; \( p < 0.001 \) (14% reduction)

Probability of Exacerbation (%)

Hazard ratio = 0.86,
(95% CI = 0.81, 0.91)
\( p < 0.0001 \) (log-rank test)

LAAC=long-acting anticholinergic

Kaplan-Meier curves show a significant survival benefit with ICS versus placebo

Comparison of Kaplan-Meier survival curves between patients treated with inhaled corticosteroids and placebo in COPD

ICS significantly reduced all-cause mortality by 27% compared with placebo (HR = 0.73; 95% CI: 0.55, 0.96; log rank p=0.039)
TORCH: All Cause Mortality by 3 Years

Rate of Exacerbations

<table>
<thead>
<tr>
<th></th>
<th>Plc</th>
<th>SAL</th>
<th>FP</th>
<th>SFC</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.13</td>
<td>0.97</td>
<td>0.93</td>
<td>0.85</td>
</tr>
</tbody>
</table>

* p< 0.001 vs Plc,
† p=0.002 vs SAL,
# p=0.024 vs FP

Efficacy and tolerability of budesonide/formoterol added to tiotropium in patients with COPD

Mean number of severe exacerbations

PDE4 Inhibition: A New Option for reducing COPD Exacerbations
PDE4 is Widely Distributed and Expressed in Key Inflammatory Cells Involved in COPD

<table>
<thead>
<tr>
<th>Leukocyte</th>
<th>PDE</th>
<th>Structured Cells</th>
<th>PDE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mast Cells</td>
<td>3, 4</td>
<td>Airway Smooth Muscle</td>
<td>1, 2, 3, 4, 5, 7</td>
</tr>
<tr>
<td>Eosinophils</td>
<td>4</td>
<td>Epithelial Cells</td>
<td>1, 2, 3, 4, 5, 7, 8</td>
</tr>
<tr>
<td>Neutrophils</td>
<td>4</td>
<td>Endothelial Cells</td>
<td>2, 3, 4, 5</td>
</tr>
<tr>
<td>Monocytes</td>
<td>4</td>
<td>Sensory Nerve</td>
<td>1, 3, 4</td>
</tr>
<tr>
<td>Macrophages</td>
<td>1, 3, 4, 7</td>
<td>Cholinergic Nerves</td>
<td>1, 3, 4</td>
</tr>
<tr>
<td>T-Cells (CD4+ and CD8+)</td>
<td>1, 3, 4, 7</td>
<td>Fibroblast</td>
<td>1, 2, 3, 4, 5, 7, 8</td>
</tr>
<tr>
<td>Dendritic Cell</td>
<td>1, 3, 4, 7</td>
<td>Pulmonary Artery Smooth Muscle</td>
<td>1, 3, 4, 5</td>
</tr>
</tbody>
</table>

Adapted from: Giembycz MA. *Monaldi Arch Chest Dis.* 2002;57:48-64.
Biochemistry of PDE4 Inhibition

PDE4 Inhibitors: Anti-inflammatory Action in COPD

• PDE4 inhibitors reduce activity of:
  ▪ Neutrophils
  ▪ Macrophages
  ▪ CD8+ T-lymphocytes

• PDE4 inhibitors reduce expression of multiple inflammatory mediators:
  ▪ Cytokines
  ▪ Chemokines
  ▪ Reactive oxygen species (ROS)
  ▪ Matrix metalloproteinases (MMPs)

Roflumilast Reduced Exacerbations when ADDED to BRONCHODILATORS
Roflumilast Improved Lung Function when ADDED to BRONCHODILATORS
### Incidence of AEs (≥ 2.5%) (Independent of investigator causality assessments)

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>AURA/HERMES 1 year</th>
<th>HELIOS 6 months</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Roflumilast (n=1547)</td>
<td>Placebo (n=1545)</td>
</tr>
<tr>
<td>COPD</td>
<td>10%</td>
<td>13%</td>
</tr>
<tr>
<td>Weight loss</td>
<td>10%</td>
<td>3%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>8%</td>
<td>3%</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>6%</td>
<td>6%</td>
</tr>
<tr>
<td>Nausea</td>
<td>4%</td>
<td>2%</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>4%</td>
<td>4%</td>
</tr>
<tr>
<td>Headache</td>
<td>3%</td>
<td>2%</td>
</tr>
<tr>
<td>Back pain</td>
<td>3%</td>
<td>2%</td>
</tr>
</tbody>
</table>


Change in Body Weight by Baseline BMI
M2-124 & M2-125 pooled analysis

CI: -2.4, -1.9 CI: -2.8, -1.2 CI: -2.1, -1.4 CI: -2.5, -1.7 CI: -3.9, -2.3

underweight: -2.1 1.3 -0.7 -1.6 -2.0 -0.5
normal: 0.1 0.1 0.1
overweight: 0.1 0.1
obese: -3.6

n=3008 n=261 n=1177 n=937 n=633

placebo roflumilast 500µg

Body Weight - Weight decrease by AE pattern*
M2-124 & M2-125 pooled analysis

Data on file

### Canadian Respiratory Guidelines
#### Optimal Pharmacotherapy

**Increasing Disability and Lung Function Impairment**

**Mild**
- SABD prn
  - persistent dyspnea
  - LAAC + SABD prn
  - or
  - LABA + SABD prn

**Moderate**
- LAAC or LABA + SABA prn

- persistent dyspnea
  - LAAC + LABA + SABA prn

- LAAC + ICS/LABA + SABA prn

**Severe**
- Frequent AECOPD
  - (> 1/year)
- Infrequent AECOPD
  - (< 1/year)

- LAAC + Daxas + LABA

- SABA prn

- persistent dyspnea
  - LAAC + ICS/LABA
  - SABA prn +/- Theophylline

**Modified from**
O’Donnell DE, et al. Can Respir J. 2006;13(Suppl A):1A-8A
Strategies for AECOPD Prevention

- Smoking cessation
- Annual influenza vaccination
- Pneumococcal vaccine once and consider every 5-10 years
- Self-management education
- Long-acting anticholinergics and/or LABA
- ICS/LABA if ≥ 1 AECOPD/yr average
- Roflumilast if taking LABD, ≥ 1 AECOPD/yr average and chronic bronchitis phenotype
- Pulmonary rehabilitation
- Proper treatment of exacerbations including systemic steroids and the right antibiotic
What about Mucolytics?

Eg. N-acetylcysteine (NAC) and carbocisteine,

-A systematic review suggested that NAC significantly reduces the odds of COPD exacerbations, although it was unclear whether this benefit was significant in patients already taking ICS.¹

-A placebo controlled one-year trial demonstrated a 24.5% reduction in AECOPD in patients taking carbocisteine.²

Self-Management
# Early Treatment of Exacerbation: Self-management Programs

Exacerbations requiring hospital admissions

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment n/N</th>
<th>Control n/N</th>
<th>Odds Ratio M-H, Fixed, 95% Cl</th>
<th>Weight</th>
<th>Odds Ratio M-H, Fixed, 95% Cl</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bourbeau 2003</td>
<td>31/96</td>
<td>48/95</td>
<td></td>
<td>35.7%</td>
<td>0.47 [0.26, 0.84]</td>
</tr>
<tr>
<td>Boxall 2005</td>
<td>5/23</td>
<td>5/23</td>
<td></td>
<td>4.3%</td>
<td>1.00 [0.25, 4.06]</td>
</tr>
<tr>
<td>Coultas 2005a</td>
<td>6/49</td>
<td>3/26</td>
<td></td>
<td>3.8%</td>
<td>1.07 [0.24, 4.68]</td>
</tr>
<tr>
<td>Coultas 2005b</td>
<td>5/51</td>
<td>2/25</td>
<td></td>
<td>2.6%</td>
<td>1.25 [0.23, 6.94]</td>
</tr>
<tr>
<td>Gallefoss 1999</td>
<td>3/31</td>
<td>4/31</td>
<td></td>
<td>3.9%</td>
<td>0.72 [0.15, 3.54]</td>
</tr>
<tr>
<td>Littlejohns 1991</td>
<td>12/68</td>
<td>14/65</td>
<td></td>
<td>12.9%</td>
<td>0.78 [0.33, 1.84]</td>
</tr>
<tr>
<td>Monninkhof 2003</td>
<td>15/127</td>
<td>16/121</td>
<td></td>
<td>15.8%</td>
<td>0.88 [0.41, 1.87]</td>
</tr>
<tr>
<td>Rea 2004</td>
<td>18/83</td>
<td>20/52</td>
<td></td>
<td>21.0%</td>
<td>0.44 [0.21, 0.95]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>528</strong></td>
<td><strong>438</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Total events: 95 (Treatment), 112 (Control)
Heterogeneity: χ²=4.35, df=7 (P=0.74); I²=0.0%
Test for overall effect: Z=2.68 (P=0.0074)

OR: 0.64 (0.47, 0.89)
Patient Self-education

[Image of a plan of action for COPD flare-up]

I FEEL WELL

MY SYMPTOMS
• I feel short of breath:
  • I cough up sputum daily: No
  • I cough regularly: No
• Yes, colour: __________________

I FEEL WORSE

MY SYMPTOMS
• I have changes in my sputum (colour, volume, consistency), not only in the morning:
• I have more shortness of breath than usual
  Note that these changes may happen after a cold or flu-like illness and/or sore throat.
  Some people feel a change in mood, fatigue or low energy prior to a flare-up.

MY ACTIONS
• I use my prescription for COPD flare up
• I avoid things that make my symptoms worse
• I use my breathing, relaxation, body position and energy conservation techniques
• If I am already on Oxygen, I use it consistently and increase from __ L/min to __ L/min
• I notify my contact person: __________________ (Tel:________) and/or see my doctor (Tel:________)

PRESCRIPTION FOR COPD FLARE-UP

1) If your sputum becomes yellowish/greenish:
   start Antibiotic: __________________ Dose: __________________ pill(s): __________ Frequency: _______ # days: _______
   if repeating antibiotics within 3 months, use the following antibiotic instead:
   start Antibiotic: __________________ Dose: __________________ pill(s): __________ Frequency: _______ # days: _______

2) If you are more short of breath than usual, take __ puffs of _______ up to a maximum of ___ puffs per day, as necessary
   if your shortness of breath does not improve:
   start PREDNISONE: __________________ Dose: __________________ pill(s): __________ Frequency: _______ # days: _______

Physician Name: __________________ Signature: __________________ License: __________________ Date: __________

I FEEL MUCH WORSE OR IN DANGER

MY SYMPTOMS
• My symptoms have worsened.
• After 48 hours of treatment my symptoms are not better.

MY ACTIONS
• I notify my contact person and/or see my doctor:
• After 5 pm or on the weekend, I go to the hospital emergency department (Tel:__________)
• I dial 911 for an ambulance to take me to the hospital emergency department.

Important Information: Make a follow-up appointment with your doctor to periodically review your plan of action or if you need to use your additional treatment twice within a short period of time (e.g. 3 months).
<table>
<thead>
<tr>
<th>I FEEL WELL</th>
</tr>
</thead>
<tbody>
<tr>
<td>MY SYMPTOMS</td>
</tr>
<tr>
<td>• I feel short of breath: ________________</td>
</tr>
<tr>
<td>• I cough up sputum daily.</td>
</tr>
<tr>
<td>• I cough regularly.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>I FEEL WORSE</th>
</tr>
</thead>
<tbody>
<tr>
<td>MY SYMPTOMS</td>
</tr>
<tr>
<td>• I have changes in my sputum (colour, volume, consistency), not only in the morning</td>
</tr>
<tr>
<td>• I have more shortness of breath than usual</td>
</tr>
<tr>
<td>Note that these changes may happen after a cold or flu-like illness and/or sore throat. Some people feel a change in mood, fatigue or low energy prior to a flare-up.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>MY ACTIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>• I use my prescription for COPD flare up</td>
</tr>
<tr>
<td>• I avoid things that make my symptoms worse</td>
</tr>
<tr>
<td>• I use my breathing, relaxation, body position and energy conservation techniques</td>
</tr>
<tr>
<td>• If I am already on Oxygen, I use it consistently and increase from ___ L/min to ___ L/min</td>
</tr>
<tr>
<td>• I notify my contact person ___________ (Tel: ____________) and/or see my doctor (Tel: ___________)</td>
</tr>
</tbody>
</table>

Template available at: http://www.respiratoryguidelines.ca/COPD-actionplan

With permission from the CTS
PRESCRIPTION FOR COPD FLARE-UP

1) If your SPUTUM becomes yellowish/greenish
start Antibiotic _______________ Dose: ___ #pills: ___ Frequency: ___ #days: ___

if repeating antibiotics within 3 months, use the following antibiotic instead
start Antibiotic _______________ Dose: ___ #pills: ___ Frequency: ___ #days: ___

2) If you are more SHORT OF BREATH than usual, take ___ puffs of ________ up to a maximum
of ___ times per day, as necessary
If your SHORTNESS OF BREATH DOES NOT IMPROVE,
start PREDNISONE _______________ Dose: ___ # pills: ___ Frequency: ___ # days: ___

_________________________________  ______________________  _____________________  _____________________
Physician Name  Signature  License  Date

I FEEL MUCH WORSE OR IN DANGER

<table>
<thead>
<tr>
<th>MY SYMPTOMS</th>
<th>MY ACTIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>• My symptoms have worsened.</td>
<td>• I notify my contact person and/or see my doctor</td>
</tr>
<tr>
<td>• After 48 hours of treatment my symptoms are not better.</td>
<td>• After 5 pm or on the weekend, I go to the hospital emergency department (Tel: ____________ )</td>
</tr>
<tr>
<td>• I am extremely short of breath, agitated, confused and/or drowsy, and/or I have chest pain</td>
<td>• I dial 911 for an ambulance to take me to the hospital emergency department.</td>
</tr>
</tbody>
</table>

Important Information: Make a follow-up appointment with your doctor to periodically review your plan of action or if you need to use your additional treatment twice within a short period of time (e.g. 3 months).

Template available at: http://www.respiratoryguidelines.ca/COPD-actionplan

With permission from the CTS
Pharmacological Treatment

1. Short-acting (beta2-agonists and anticholinergic) bronchodilators to treat wheeze and dyspnea. Continue all of your long acting bronchodilators or inhaled steroids as prescribed.
2. Prednisone (oral) → 25-50 mg once daily for 10 days for patients with moderate to severe COPD¹.
3. Antibiotic choice is prescribed based upon the presence of risk factors as below.
4. Severe AECOPD complicated by acute respiratory failure is a medical emergency. Consider consultation with an emergency specialist or respirologist.

General Recommendations

1. Patients need to be instructed to call or visit their treating physician if symptoms persist or worsen in spite of patient-initiated treatment.
2. The prescription of antibiotics and prednisone can only be renewed once unless re-evaluated by the physician.
3. To reduce the risk of antibiotic resistance, if more than one treatment is required over 3 months, the class of antibiotics should be changed on subsequent prescription.
4. Review with your patient general measures to prevent future COPD exacerbations including smoking cessation, annual influenza vaccination, pneumococcal vaccination and appropriate use of inhaled medications.

Template available at: http://www.respiratoryguidelines.ca/COPD-actionplan

With permission from the CTS
Discharge Protocol
Discharge instructions

- ACUTE:
- Oxygen
- Triple therapy likely: Spiriva, LABA/ICS, Ventolin prn
- Inhaler technique
- Antibiotic
- Smoking cessation (teachable moment!)
- Nutrition
- Home Care involved?
- Return prn.....if...
Discharge instructions

- PREVENTION
- Nutrition and Hydration
- Smoking cessation
- Comorbidities
- Pulmonary Rehabilitation if available
- Osteoporosis prevention (Vitamin D at least....)
- COPD Education clinic if available
- To Prevent Exacerbations
  - Immunizations
  - Triple therapy of Spiriva and ICS/LABA
  - Daxas for those with symptoms of chronic bronchitis
- Follow up!!!!!
Education!
Accidental or intentional interruption of treatment in COPD: PRE-SPIRO

- 179 patients, mean age 62, females 23%
- Co-morbidities mean = 2.3 (54% hypertension)
- Mean number of drugs = 4.9 (SD 2.9)
- All on several inhaled treatments for COPD
  - LABA/ICS 65%
  - LAMA 44%
  - LABA 21%


SD = Standard deviation
Accidental or intentional interruption of treatment in COPD

- Age 70+
- Feeling too many drugs to take daily
- Current smoking
- COPD Stage III or IV
- Supervised by Specialist
- Feeling adequately informed about therapy!

Logistic regression models for non-adherence

0 1 3

A new perspective on ‘optimal care’ for patients with COPD

New Initiative

• College of Family Physicians Section on Respiratory Medicine
• Special interest group at CFPC
• Goals:
  - Increase level of care for patients with respiratory diseases
  - Support family physicians in giving this care
  - GPSI as per UK
  - CME
  - Curriculum