The Lung Attack Alert Study (TLAL Study)

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Original: December 2, 2009
Edmonton, AB

Revision 1: April 11, 2010
Edmonton, AB
(Web randomization, medication revision)

Revision 2: October 18, 2010
Edmonton, AB
(CAT form added)

Introduction

Chronic Obstructive Pulmonary Disease (COPD) is the 4th leading cause of mortality in Canada[1], and accounts for significant morbidity in patients affected by the disease. COPD is now seen as a disease that is both preventable and treatable. In order to better facilitate treatment for these patients, a number of national and international consensus guidelines have been developed to help physicians in the diagnosis and chronic management of these patients.

The Canadian Thoracic Society published guidelines on the management of COPD in 2007[2] (updated in 2008) to help physicians optimize the care of patients with COPD. The guidelines were based on current evidence within the medical literature. Despite the availability of guidelines for COPD (as well as other specialties), implementation of guidelines into daily clinical practice, remains a challenge.

Patients who experience an Acute Exacerbation of COPD (AECOPD) have an increased risk of mortality[3]. They represent an important subset of patients with COPD who need their management urgently optimized, to guideline standards, in order to improve their survival. These patients most often present to their local emergency departments (ED) for the acute episode. For patients who are admitted to hospital, an opportunity exists to re-evaluate their chronic management and therefore optimize their care. However, for patients who are not admitted to hospital, follow up care is often left to their primary care physician (PCP), if they have one. Information regarding how frequently this occurs, and what the outcomes of these follow up visits with their PCP is unknown. Although the national rate of patient follow up of patients by their PCP within the first month following an AECOPD is unknown, locally it is only 30%[4]. This low rate of follow up represents a lost opportunity for reassessment of both the acute and chronic management of these patients, as well, represents a delay in optimizing their care to help improve their long term survival. One of the factors contributing to this low rate of follow-up, is poor or delayed communication between the ED and PCP.

It is our belief that improving the communication between the ED and the PCP regarding patients, who are discharged from the ED after being treated for their AECOPD, will improve the rates of patient follow up. Furthermore, if the communication highlights care gaps in the chronic management of COPD, this may result in an adjustment in management such that the patients' treatment will be more in keeping with current guideline recommendations.

Methods

This study will be a 1 year randomized controlled trial to assess the impact of the "Lung Attack Alert" on rates of follow up by PCP of their patients following presentation to the ED for an AECOPD. The tool being assessed is labeled as the "Lung Attack Alert"(see **Appendix 1**). This is a novel information sheet that is intended for the PCP. The Lung Attack Alert summarizes the following points:

a) that the PCP's COPD patient has had a presentation to the ED for an AECOPD but did not require a prolonged hospital admission;

b) a description of the discharge management from the ED will be provided;

c) a recommendation to the PCP to follow up with the patient within 1-2 weeks after discharge from the ED;

d) Care gaps identified in the patients chronic management of COPD based on the Canadian Thoracic Society 2007(updated 2008) guidelines will be highlighted for the PCP to address at the next outpatient follow up

Each Lung Attack Alert will be **individualized** to the patients care gap(s) identified during screening.

This study will enroll consecutive patients who present to the ED at the University of Alberta Hospital and the North East Community Center (both located in urban Edmonton), who present with an AECOPD, but who do not require admission to hospital.

ED physicians or the study coordinator will screen patients who present to the ED with an AECOPD, who have recovered from the acute event and are considered safe for discharge. All patients will receive usual care within the ED prior to screening and entry into the study. This may consist of the use of any or all of the following: oxygen, acute bronchodilators (+/- use of nebulizers or MDI), administration of oral/IV corticosteroids, intravenous fluids, non-invasive ventilation (NIV), oral or intravenous antibiotics as required.

Patients will be screened by either the ED physicians who will notify our study coordinator regarding the eligibility of a patient or directly by the study coordinator. Eligible patients (**Appendix 2**) will be provided with a patient information sheet (**Appendix 3**) outlining the rationale for the study. If the patient is agreeable to participate, a consent form will be signed and witnessed by either the ED physician or study coordinator (**Appendix 4**). To be enrolled into the study patients must satisfy all inclusion and exclusion criteria.

Inclusion:

Appropriately signed and dated informed consent has been obtained

ED patients presenting with an acute exacerbation of COPD requiring treatment in the ED;

Previous physician-diagnosis of COPD (e.g., emphysema, chronic bronchitis or COPD) either previously or within the ED;

Age >40 years of age;

Current or former smokers of more than 10 pack years (number of packs of cigarettes {or pipe and/or cigars) smoked per day X the number of years of smoking);

FEV_1/FVC ratio < 0.7 for age, sex and height (either known or determined within the ED);

Patients can read and comprehend English language.

Exclusion:

Patients presenting for prescription renewal;

Patients who require hospitalization;

Patients who ***do not*** have a primary care physician or patients for whom a family physician cannot be found;

Patients who have already been enrolled in the study;

Patients with a ED physician-diagnosis of primary asthma, pneumonia, HIV/AIDS, immuno-compromise, or life expectance of < 90 days.

Patients who, in the opinion of the investigator, should be excluded.

Using concealment of allocation, patients will be randomized using computerized random numbers tables to control and intervention groups. Randomization will be in a 1:1 distribution between the control and intervention group.

Upon enrollment into the study, basic information regarding the patient and their disease status will be collected. An ED chart review will be completed to document ED care. **We will complete the COPD Assessment Test (CAT), a**

new questionnaire for people with COPD. It is designed to measure the impact of COPD on a person's life and is freely available on the internet (www.catestonline.org). See Appendix 6 for the complete set of information to be collected.

All patients enrolled in the study will be discharged home with a standardized protocol for the outpatient management of the AECOPD (**Appendix 5**). This will include a standardized length and dose of both oral corticosteroids (oral prednisone 50 mg once daily X 10 days) and antibiotics (oral Doxycycline 100 mg twice daily X 5 days or Levofloxacin 750 mg once daily X 5 days). The dosage and length of therapy is based on current standards and recommendations outlined in the CTS 2007 (updated 2008) consensus guidelines. The standardized medications will be provided for the patient at no cost to the patient themselves by the Central Research Pharmacy at the University of Alberta Hospital).

After normal working hours(see below), when research staff are not available, patients who are eligible and who have consented to enter the study but have been discharged from the ED, will be contacted by the study coordinator the next morning by phone. Randomization will take place at that time and the appropriate process will take place thereafter. Those patients who are discharged from the ED will receive the outpatient treatment package (by the consenting ED physician) used in the study (Appendix 5) for the medical management of their AECOPD. The outpatient medication package will be readily available in the ED, in a reserved area for the study. This is to ensure that there is no delay in their treatment, as well, that their acute management does not impact the effect of the Lung Attack Alert.

As per the above randomization process, patients will be randomized into either the **control** group or the **intervention** group using a web-based randomization process (Epidemiology Coordinating and Research {EPICORE} Centre, Edmonton, AB; http://www.epicore.ualberta.ca).

The **control** group will be discharged from the ED, with the standardized outpatient protocol (Appendix 5) and will be advised to follow up with their PCP. They will be provided with general information regarding COPD in the form of the "Breathworks" program pamphlets established by the Canadian Lung Association. These are readily available in print and online, and they are information guides for patients with COPD. The patients will then be contacted by a research staff member unaware of the allocation of treatment at day 30 and 90 post discharge from the ED to discuss the primary and secondary outcomes (**Appendix 7**).

The **intervention** group will also be advised to follow up with their PCP, along with the standardized outpatient protocol for their acute exacerbation (Appendix

5). They will be provided with general information regarding COPD in the form of the "Breathworks" program. The intervention group will have the Lung Attack Alert form completed by the research study staff. The form will highlight the information already discussed earlier. This will then be faxed to their primary care physician by the study coordinator. The patients will then be contacted by a research staff member unaware of the allocation of treatment at day 30 and 90 post discharge from the ED to discuss the primary and secondary outcomes (**Appendix 7**).

Outcomes

The **Primary Endpoint** of this study is the rate of follow up of the patient by their primary care provider for review of the acute and chronic management of their COPD and addressing any issues on the Lung Attack Alert, within the first 90 days after discharge from the ED. The study coordinator will contact all patients enrolled on day 30 after admission to the ED to determine if a follow up visit has occurred and if any of the recommendations noted on the Lung Attack Alert have been implemented.

A number of **Secondary Endpoints** will be collected. These include 1) relapse of the AECOPD requiring acute intervention (ED or clinic) within the 90-day study period; 2) admission to the hospital within the 90-day study period; 3) review and adjustment of the management of COPD at day 90 post discharge from the ED 4) Proportion of patients who completed their acute management within the 90-day study period and 5) length of stay within the ED.

The study coordinator will contact the PCP of patients in the intervention group to survey the usefulness of the Lung Attack Alert once the study is complete. This survey will assess the clinical utility of the alert and the ease of use of the information provided in the alert to aid in clinical management.

Statistics

Sample Size Considerations:

Calculations for the estimated sample size were completed using a formula for calculation of dichotomous response variables with two independent samples. We assumed $\alpha = 0.05$ (accepted standard value), power $(1- \beta) = 0.80$, and that 30% of patients in the control group would see their PCP within 30-days. This estimate of 30-day follow-up is taken directly from recent administrative data from Alberta. The sample size was therefore calculated to detect a 30% absolute difference in 30-day follow-up (30% of the standard-care vs. 60% of enhanced care groups). In addition, we used 1-tailed estimates due to the assumption that the intervention will not ***decrease*** the follow-up of patients with COPD. The total sample size was estimated at 98 (49/group) patients; however, if we assume ~10% attrition (see previous COPD study), the total sample size is estimated at 110 patients.

Recruitment plan:
We have full-time research staff nurses at the UAH (coverage 16 hours/day; 08:00-24:00 M-F; 10:00-18:00 S&S) and at the NECHC (8 hours/ day; 10:00-18:00). We will increase our coverage if the numbers indicate the need to do so. We anticipate 5/month at the UAH and 4/month at the NECHC. Approximately one year of enrolment (February 2010-March 2011) should provide the numbers required for this study.

Principal analysis of the primary outcome measure:
The final analysis will be performed on an "intention to treat" basis. Using this approach, patients will be included in the analysis according to the group to which they were randomized. Baseline characteristics in the two treatment arms will be compared using univariate descriptive statistics. The principal analysis of 30-day relapse will be done using an unadjusted χ^2 comparing the proportion of events in each treatment group. A logistic regression procedure will be employed to adjust raw relapse proportions using significant co-variates (such as patient use of inhaled steroids, current smoking status, etc) which may influence outcomes

We chose the proportion of PCP visits within 30 days as a primary outcome measure rather than survival time to relapse. We believe that it is more relevant to both patients and physicians to know if the enhanced intervention will stimulate a PCP visit rather than examining relapse (which may be affected by age, severity, type of treatment received, smoking status, etc). Therefore, unadjusted χ^2 followed by logistic regression procedures were chosen over log-rank tests followed by Cox proportional hazards modelling. Both alternative analytic approaches mentioned will still be performed and reported.

Principal analysis of the secondary outcome measure:
All secondary outcome measures will be assessed at 30 days and 90 days and will be analysed using an "intention to treat" analysis. Patients will be contacted to see if they have had an urgent visit (to ED or their PCP). If they describe a relapse (an unscheduled visit for worsening COPD), then we will obtain further information from their medical records and/or treating physician. Those patients who relapse within the first 30 days of the trial will have measurements of oxygenation, airflow obstruction, dyspnea, and quality-of-life done on the day of relapse (either from the family physician or the EDs where they attend). These values will be counted as the last day values for purposes of the analysis (i.e., endpoint analysis, with the last observation carried forward).

Continuous outcome measures including absolute and percent changes in FEV_1, oxygen saturation, Transitional Dyspnea Index scores, and changes from Day 1 to Day 30 in the scores of the four components of the Chronic Respiratory Questionnaire will be analysed using either parametric procedures (independent t tests) initially, or with non-parametric methods (Wilcoxon Rank Sum) if the data is not normally distributed. At 90 days, the proportion of patients who achieve

compliance with recommendations (for LAAC, LABA/ICS combinations, and rehabilitation referral), relapse and are hospitalized will be compared using unadjusted χ^2 tests followed by logistic regression procedures. Survival analyses (log-rank tests followed by Cox proportional hazards modelling) will be used to compare time to relapse.

Relapse Assessment and Adjudication:

Each patient who relapses will have assessment to verify the location, treatment received and the severity. In most cases, this will occur at the primary ED setting; however, in some cases, patients may relapse back to their Family Physician's office. In each case, study staff will either collect ED data (with hospital relapse through direct patient chart review) or primary care data (through contact with the Family Physician's office). A relapse chart review will be completed and adjudication will be made independently by two study physicians (MB, BHR). Patient will be placed into one of the following relapse categories: relapse without treatment-discharged; relapse with acute/ED treatment and no chronic management change-discharged; relapse with acute/ED treatment and chronic management change-discharged; relapse with acute/ED treatment and chronic management change-admitted; died.

Ethics, informed consent and regulatory considerations

The full program will be reviewed and the patient consent form approved by the University of Alberta Research Ethics Board.

It is the responsibility of the ED physician/designee to provide each subject with verbal and written study related information, using the IRB/IEC approved informed consent document.

Each subject must voluntarily provide written informed consent (including consent for the use and disclosure of research-related health information). The consent must be obtained prior to performing any study-related procedures that are not part of normal patient care, including screening. A copy of the signed informed consent must be given to the study subject and also placed on the chart.

Safety

Serious Adverse Event (SAE) Reporting Requirements:

Adverse event information is not expected to be available from the source data used, and therefore will not be routinely collected in this study. However, should the Investigator/Sponsor become aware of a serious adverse event attributable to a GSK marketed product during the conduct of the study, it must be reported to GlaxoSmithKline within 24 hours of first identification.

For detailed reporting procedure and SAE definition, please see **Appendix 9**

Budget (See **Appendix 8** for full details)

The **Total Budget** for this project will be **$151,797.10**

The Budget is based on the following:

Study Cost: $116,767.00($1061.52/patient)

Institutional Costs: The University of Alberta Institutional Costs is 30% in addition to the expected costs of the Study. For our study this totals: **$35,030.10**

The total of **$151,797.10** is required to complete this study. We believe that our budget projections are based on realistic amounts that will be required to conduct a 2-site study that will involve emergency departments within Edmonton. It is estimated the study will require 12 months to enroll 110 patients and complete follow-up. We anticipate it will take the coordinator one month to organize the study supplies and sites in advance of enrollment. Another two to three months will be needed to complete data entry and analysis for the 110 patients and to prepare a manuscript for publication.

Pilot Work:

An "Emergency COPD Research Program" has been developed in Edmonton over the past 2 years. Dr. Bhutani has extensive experience with the management of clinical COPD through the Lung Health Centre and the Edmonton General Hospital. Dr. Rowe has extensive experience in clinical trials and Airway Disease research. In addition, his research team is already in place to assist with the recruitment and follow-up of these patients.

Anticipated Results:

The results of this study will be used widely by clinicians to inform decisions regarding the care of patients seen in the emergency department with COPD exacerbations. If our study shows that addition of LAL referral to corticosteroids, antibiotics and bronchodilators does improve follow-up and evidence-based care. its use should be encouraged in this patient population. This would be important information, since it is widely recognized that efforts to improve follow-up, medication review, and prevention/rehabilitation programs are important. Conversely, if our study shows LAL referral does not improve follow-up and other outcomes, then renewed efforts will be required to seek interventions that are effective. Thus, the results of this trial, whether positive or negative, should help to standardize and improve care for COPD outpatients who present with an exacerbation of their disease.

Time Lines

HREB Review: February 16, 2010 (Pro00011325)

Study Set Up: March 2010

First Patient In: April 12, 2010

Last Patient Out: July 2011

Data Entry/Analysis: August 2011

Abstract/Manuscript: October 2011

References:

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[2] DE O'Donnell, S Aaron, J Bourbeau et al. Canadian Thoracic Society recommendations for management of chronic obstructive pulmonary disease-2007 update. Can Respir J 2007;14(Suppl B): 5B-32B

[3] Seemungal TA, Donaldson GC, Paul EA, Bestall JC, Jeffries DJ, Wedzicha JA. Effects of exacerbation on quality of life in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 1998;157:1418-22

[4] Rosychuk RJ, Rowe BH, Voaklander DC, Klassen TP, Senthilselvan,A, Marrie TJ. Visits to Alberta Emergency Departments for Chronic Obstructive Pulmonary Disease (COPD): April 1, 1999 to March 31, 2005. CANA website