

# Is Acute Exacerbation of COPD (AECOPD) Related to Viral Infection Associated with Subsequent Mortality or Exacerbation Rate?



Omar Kherad<sup>\*,1</sup>, Pierre-Olivier Bridevaux<sup>2</sup>, Laurent Kaiser<sup>3</sup>, Jean-Paul Janssens<sup>2</sup> and Olivier T. Rutschmann<sup>4</sup>

<sup>1</sup>Department of Internal Medicine and University of Geneva, La Tour Hospital, Geneva, Switzerland

<sup>2</sup>Division of Pulmonary Diseases, Geneva's University Hospitals and University of Geneva, Geneva, Switzerland

<sup>3</sup>Central Laboratory of Virology, Division of Infectious Diseases, Geneva's University Hospitals and University of Geneva, Geneva, Switzerland

<sup>4</sup>Department of Community, Primary Care and Emergency Medicine, Geneva's University Hospitals and University of Geneva, Geneva, Switzerland

**Abstract:** *Background:* There is a growing interest in better defining risk factors associated with increased susceptibility to exacerbation in patients with COPD.

*Objectives:* The aim of the study was to determine whether identification of a respiratory virus during a severe acute exacerbation of COPD (AECOPD) increases the risk of subsequent exacerbations and mortality during a one-year follow-up.

*Methods:* Secondary analysis of 86 COPD patients admitted for AECOPD between June 2007 and December 2008 at Geneva's University Hospital who were followed up for 1 year. Fifty-one percent of index AECOPD were related to viral infection. Rate of AECOPD, time to next AECOPD, and all-cause mortality were compared between patients with vs without viral index AECOPD.

*Results:* Eighty-one cases were included in this secondary follow-up analysis. Mean exacerbation rate was 1.9 AECOPD per person-year for patients with viral index AECOPD vs 4.0 AECOPD per person year for those with non-viral index AECOPD. Incidence rate ratio (IRR) for subsequent AECOPD during one year follow up was lower for patients with viral index AECOPD (IRR 0.57; [CI 95% 0.39-0.84]), after controlling for previous exacerbations, and was strongly associated with the number of exacerbations in the year preceding the index AECOPD. During the one-year follow-up period, 16 patients (19%) died. In a Cox regression model, patients with a proven viral infection did not have a higher mortality (HR 0.56 [CI 95% 0.20 -1.58]).

*Conclusions:* Viral AECOPD was not associated with a higher rate of subsequent exacerbations or mortality during the following year.

**Keywords:** COPD, exacerbation, phenotype, virus.

## INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a leading cause of disability and mortality worldwide. Acute exacerbations of COPD (AECOPD) contribute to poor quality of life and are a major cause of hospital admissions leading to significant health costs [1]. It is not entirely clear why some COPD patients experience frequent exacerbations, while others remain free. AECOPD are generally considered to become more frequent when COPD is advanced and a

history of previous exacerbations best predicts the subsequent occurrence of AECOPD [2,3].

Recently, there has been a growing interest in better defining COPD phenotypes associated with increased susceptibility to exacerbation, including milder forms of COPD, and identifying factors that might correlate with these phenotypes [4]. Recent studies explored the hypothesis that there may be a “frequent-exacerbation” phenotype independent of disease severity, implying the existence of an underlying mechanism (genetic, biologic or behavioural) that determines susceptibility to recurrent exacerbations [5-7]. Microaspiration from gastroesophageal reflux, psychological factors, such as perception of dyspnea and adherence to medication have been proposed as predisposing factors [5,6]. A greater susceptibility to viral respiratory tract infections

\*Address correspondence to this author at the Department of Internal Medicine and University of Geneva, La Tour Hospital, 3 avenue J.-D. Maillard 1217 Geneva, Switzerland; Tel: +41 22719.60.99; Fax: +41 22 719.67.01; E-mail: omarkherad@gmail.com

has also been highlighted. This hypothesis was sustained by a potential higher sensitivity to viral infections that may be explained by an up regulation of intercellular adhesion molecule (ICAM-1), which is the major receptor for some viruses [8,9]. Simultaneously, viral infections have been confirmed as a cause of AECOPD and several studies suggest that viral AECOPD are more severe, and are associated with prolonged recovery time and greater morbidity [10-19].

Using previously published data, the aim of this study was to determine whether identification of a respiratory virus during an index severe acute exacerbation of COPD (AECOPD) is associated with an increased risk of subsequent exacerbations and mortality during a one-year follow-up in patients who survived initial AECOPD.

## MATERIALS AND METHODS

This work reflects secondary analysis from a previous published study [18]. COPD patients admitted for AECOPD ( $n=86$ ) between June 2007 and December 2008 at Geneva's University Hospital were followed up for 1 year. Detailed inclusion criteria, patients characteristics, procedure and virological samples have already been reported [18].

Briefly, after systematic virological sampling with nasopharyngeal swabs (individual two steps real-time Taqman® based RT- PCR or PCR assays for 18 distinct respiratory viruses found in the community obtained at index admission and 4 months later in stable condition), original study found that 51% ( $n=44/86$ ) of index AECOPD were associated with viral infection versus 11% ( $n=7/71$ ) in stable condition [18]. Bacteriological analyses of sputum samples at index admission were available in 61 cases (29% were unable to produce sputum) and 39 of 61 (64%) met microscopic criteria for bacteriological validity. Of these 39 cases, 20 (51%) had a positive culture. Only 7 (8%) of the 20 cases with a documented bacterial infection or colonisation were co-infected with a virus. Both virus-positive and virus-negative groups were comparable regarding baseline characteristics, except that patients with viral infection reported less frequent COPD exacerbations during the previous year and a shorter duration of symptoms before admission. We found no statistically significant difference between patients with and without virus-associated AECOPD in terms of time to clinical recovery, length of hospital stay, or 4-months mortality.

One year after the index AECOPD, for the purpose of this new study, patients who survived initial AECOPD were contacted directly by phone and/or through their primary care physician (PCP) to collect information about subsequent AECOPD and mortality ( $n=81$ ). Five patients could not be contacted and were excluded from analysis. AECOPD was considered when patients or their PCP reported admission or outpatient corticosteroid and/or antibiotic therapy for an acute respiratory problem. Death reported to be of respiratory cause was also considered as AECOPD. Patients, who died during the index AECOPD (3 cases) were excluded for analysis of AECOPD incidence.

## Statistical Analysis

The event rate of exacerbation (number of AECOPD/person-times of follow up) was analysed with a

Poisson regression model. Event rates were calculated for categories of patients with or without viral AECOPD and according to number of AECOPD (0, 1, 2 or more AECOPD) during the year preceding the index AECOPD. Cox regression model was used to analyse all-cause mortality and time to first AECOPD, according to the presence or absence of viruses at initial AECOPD. Results are presented as hazard ratios (HR) with 95% confidence intervals (95% CI). All statistical analyses were performed using SPSS (version 15.0 for Windows, Chicago, IL,) and STATA version 11.

## RESULTS

Patients' characteristics were similar in both groups (viral or non-viral index exacerbation) except for AECOPD episodes during the preceding year, which were more frequent in subjects with non-viral index AECOPD. ( $1.4 \pm 1.6$  vs  $0.8 \pm 1.0$ ,  $p=0.04$ ) [18].

Overall, we observed 114 AECOPD for a total of 14'959 days of follow-up. Mean exacerbation rate was 1.9 AECOPD per person-year for patients with viral index AECOPD and 4.0 AECOPD per person-year for those with non-viral index AECOPD. Patients with viral index AECOPD were less likely to have subsequent AECOPD during one year follow up (Incident rate ratio (IRR) 0.57; [CI 95% 0.39-0.84]), after controlling for previous exacerbations. In fact, IRR of exacerbations was strongly associated with the number of exacerbations in the year preceding the index AECOPD (Table 1). Patients with 2 or more previous exacerbations had a 3 fold excess risk of recurrent exacerbation in the following year (IRR 3.26; [CI 95% 2.09-5.06]). AECOPD rate during follow-up was: 5.2 per person-year for those who reported  $\geq 2$  AECOPD during the preceding year, vs 3.6 per person-year for those with 1 exacerbation and 1.5 per person-year for those without any exacerbation.

**Table 1. Incidence rate ratio (IRR) of exacerbations during 1-year follow-up.**

	IRR (95% CI)
Presence of virus at index exacerbation:	
Non viral index AECOPD	ref
Viral index AECOPD	0.57 (0.39-0.84)*
Number of exacerbations during the year preceding the index exacerbation:	
No AECOPD	ref
One AECOPD	2.12 (1.28- 3.50)
Two or more AECOPD	3.26 (2.09 - 5.06)

\*Adjusted for number of previous exacerbations; ref= reference.

During follow-up, 16 patients died; 6 (7.3%) had viral index AECOPD and 10 (12 %), non-viral index AECOPD. In a Cox regression model, mortality was not higher for patients with a proven viral infection (HR 0.56 [95% CI 0.20 -1.58]) after adjustment for severity of obstruction, number of previous exacerbations and age. Similarly, time to first exacerbation did not differ between groups (log rank  $p= 0.59$ ).

Subgroup analysis of patients with virus identified in their upper viral respiratory tract at 4 months after the index

hospitalization (n=8 of 71) did not show a relation between prolonged viral shedding and frequent exacerbations ( $p=0.93$ ).

## DISCUSSION

In our study, viral related AECOPD leading to hospitalization was not associated with a higher rate of exacerbations when compared to non-viral AECOPD, during a 1-year follow-up. These results do not support the hypothesis that COPD patients who have a documented viral infection have a higher risk of recurrent AECOPD. To the best of our knowledge, our study is the first work that looks for an association with an index viral AECOPD and subsequent exacerbation. Previous studies suggest that viral AECOPD are more severe, and are associated with prolonged recovery time [10-19]. However, only one study reported a trend for more frequent exacerbations in stable COPD in whom viruses were detected, suggesting chronic viral shedding as a predisposing factor for recurrent AECOPD [17]. Prolonged shedding has been mainly described for RSV and the small number of cases observed in our study precludes any further conclusions. We can however hypothesize that the seasonal pattern of RSV epidemics, varying substantially every year, might explain this discrepancy. Indeed, several studies, even in Switzerland, reported a biennial activity of RSV that could underestimate the prevalence of RSV in our COPD population study in comparison with others studies.

Furthermore, the observation that viral AECOPD may confer a relative protection against further exacerbation compared to non viral AECOPD is intriguing. It has previously been reported that patients with frequent exacerbations may have increased airway inflammation in the stable state. It remains not clear whether our results reflect that people with a chronic inflammation of their lung are protected against viral infection. Interestingly, a recent study reported that COPD patients prone to exacerbation had significantly lower concentrations of rhinovirus antibodies (anti-VP1 IgG1) [20]. In our study, rhinovirus was the main infectious agent and we may hypothesize, that patients with index viral AECOPD were partly immunised against rhinovirus during the following year, suggesting a “refractory period” and highlighting the importance of humoral immunity against rhinoviruses. The extent to which anti-microbial immunity in COPD is associated with exacerbations needs further investigations.

Our findings confirm that the most reliable predictor of exacerbations in an individual patient seems to be a history of frequent exacerbations. Indeed, number of exacerbations during the year preceding the initial AECOPD was strongly associated with future exacerbation rate, suggesting that patients with frequent exacerbations have a distinct phenotype regardless the presence of viruses. This confirms that “frequent exacerbators” ( $\geq 2$  AECOPD/year) may be proposed as one of clinically distinct phenotypic characteristics of COPD disease [4,5,21].

Our study has a main limitation: the role of bacterial infection or co-infection may have been underestimated during the initial sampling. Although systematically sought for, sputum samples for bacterial analysis were available in less than half of the index AECOPD cases. These limitations

related to bacterial sampling are inherent to the population studied, in whom sputum analysis may be difficult to collect during an AECOPD. For the same reason, virological samples were collected from the URT rather than sputum. However, the concordance between naso-pharyngeal swabs and lower respiratory tract sampling has been found to be high, in particular for respiratory viruses.

## CONCLUSION

Our study suggests that a documented respiratory virus during an AECOPD is not predictive of subsequent exacerbation or mortality rates during the following year. Understanding the mechanistic basis for frequent exacerbations and the exact role of viruses might lead to more effective preventive therapy and warrants further investigations.

## CONFLICT OF INTEREST

The author confirms that this article content has no conflict of interest.

## ACKNOWLEDGEMENTS

Declared none.

## REFERENCES

- [1] Vestbo J, Agusti A, Anzueto A, et al. The Global Strategy for Diagnosis, Management and Prevention of COPD (updated 2010). Global Initiative for chronic obstructive pulmonary disease (GOLD). [www.goldcopd.com](http://www.goldcopd.com). Date last updated: November 2010. Date late accessed: July 2011.
- [2] Donaldson GC, Wedzicha JA. COPD exacerbations. 1: Epidemiology. *Thorax* 2006; 61(2): 164-8.
- [3] Agusti A, Calverley PM, Celli B, et al. Characterisation of COPD heterogeneity in the ECLIPSE cohort. *Respir Res* 2010; 11: 122.
- [4] Garcia-Aymerich J, Gomez FP, Benet M, et al. Identification and prospective validation of clinically relevant chronic pulmonary disease (COPD) subtypes. *Thorax* 2011; 66(5): 430-7.
- [5] Hurst JR, Vestbo J, Anzueto A, et al. Susceptibility to exacerbation in chronic obstructive pulmonary disease. *N Engl J Med* 2010; 363(12): 1128-38.
- [6] Tashkin DP. Frequent exacerbations of chronic obstructive pulmonary disease--a distinct phenotype? *N Engl J Med* 2010; 363(12): 1183-4.
- [7] Brudevaux PO, Gerbase MW, Probst-Hensch NM, Schindler C, Gaspoz JM, Rochat T. Long-term decline in lung function, utilisation of care and quality of life in modified GOLD stage 1 COPD. *Thorax* 2008; 63(9): 768-74.
- [8] Wedzicha JA, Donaldson GC. Natural history of successive COPD exacerbations. *Thorax* 2012; 67(11): 935-6.
- [9] Wedzicha JA. Role of viruses in exacerbations of chronic obstructive pulmonary disease. *Proc Am Thorac Soc* 2004; 1(2): 115-20.
- [10] Beckham JD, Cadena A, Lin J, et al. Respiratory viral infections in patients with chronic, obstructive pulmonary disease. *J Infect* 2005; 50(4): 322-30.
- [11] Rohde G, Wiethege A, Borg I, et al. Respiratory viruses in exacerbations of chronic obstructive pulmonary disease requiring hospitalisation: a case-control study. *Thorax* 2003; 58(1): 37-42.
- [12] Greenberg SB, Allen M, Wilson J, Atmar RL. Respiratory viral infections in adults with and without chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2000; 162(1): 167-73.
- [13] Borg I, Rohde G, Loseke S, et al. Evaluation of a quantitative real-time PCR for the detection of respiratory syncytial virus in pulmonary diseases. *Eur Respir J* 2003; 21(6): 944-51.
- [14] Papi A, Bellettato CM, Braccioni F, et al. Infections and airway inflammation in chronic obstructive pulmonary disease severe exacerbations. *Am J Respir Crit Care Med* 2006; 173(10): 1114-21.
- [15] Ko FW, Ip M, Chan PK, et al. Viral etiology of acute exacerbations of COPD in Hong Kong. *Chest* 2007; 132(3): 900-8.

- [16] Mallia P, Johnston SL. How viral infections cause exacerbation of airway diseases. *Chest* 2006; 130(4): 1203-10.
- [17] Seemungal T, Harper-Owen R, Bhowmik A, *et al.* Respiratory viruses, symptoms, and inflammatory markers in acute exacerbations and stable chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2001; 164(9): 1618-23.
- [18] Kherad O, Kaiser L, Bridevaux PO, *et al.* Upper-respiratory viral infection, biomarkers, and COPD exacerbations. *Chest* 2010; 138(4): 896-904.
- [19] Mallia P, Footitt J, Sotero R, *et al.* Rhinovirus infection induces degradation of antimicrobial peptides and secondary bacterial infection in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2012; 186(11): 1117-24.
- [20] Yerkovich ST, Hales BJ, Carroll ML, *et al.* Reduced rhinovirus-specific antibodies are associated with acute exacerbations of chronic obstructive pulmonary disease requiring hospitalisation. *BMC Pulm Med* 2012; 12(1): 37.
- [21] Han MK, Agusti A, Calverley PM, *et al.* Chronic obstructive pulmonary disease phenotypes: the future of COPD. *Am J Respir Crit Care Med* 2010; 182(5): 598-604.

---

Received: October 22, 2013

Revised: March 14, 2014

Accepted: April 14, 2014

© Kherad *et al.*; Licensee Bentham Open.

This is an open access article licensed under the terms of the Creative Commons Attribution Non-Commercial License (<http://creativecommons.org/licenses/by-nc/3.0/>) which permits unrestricted, non-commercial use, distribution and reproduction in any medium, provided the work is properly cited.