Original Article

Respiratory viruses in acute exacerbations of chronic obstructive pulmonary disease

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ABSTRACT

Objective: Acute exacerbations of chronic obstructive pulmonary disease (AECOPD) cause significant morbidity, mortality, and an inexorable decline of lung function. Data from developed countries have shown viruses to be important causes of AECOPD, but data from developing countries like India are scant. We set out to determine the contribution of viruses in the causation of hospitalized patients with AECOPD. **Methods:** Twin nasopharyngeal/oropharyngeal swabs collected from 233 patients admitted with an acute AECOPD and tested for respiratory viruses including respiratory syncytial virus A and B, parainfluenza were (PIV) 1, 2, 3, and 4, human metapneumovirus (hMPV) A and B, influenza A and B, enterovirus, corona NL65, OC43, and 229E viruses, adenovirus 2 and 4, rhinovirus, and bocavirus, by duplex real time reverse-transcription polymerase chain reaction (qRT-PCR) using CDC approved primers and probes. Samples positive for influenza A were subtyped for A/H1N1pdm09 and A/H3N2 whereas influenza B samples were subtyped into B/Yamagata and B/Victoria subtypes, using primers and probes recommended by CDC, USA. **Results:** Respiratory viruses were detected in 46 (19.7%) cases, influenza A/H3N2 and rhinoviruses being the most common viruses detected. More than one virus was isolated in four cases consisting of hMPV-B + adeno-2 + Inf-B; rhino + H3N2, PIV-1 + rhino; and PIV-1+ hMPV-B in one case each. Ancillary supportive therapeutic measures included bronchodilators, antibiotics, steroids, and ventilation (noninvasive in 42 and invasive in 4). Antiviral therapy was instituted in influenza-positive patients. Three patients with A/H3N2 infection died during hospitalization. **Conclusions:** We conclude that respiratory viruses are important contributors to AECOPD in India. Our data calls for prompt investigation during an exacerbation for viruses to obviate inappropriate antibiotic use and institute antiviral therapy in viral disease amenable to antiviral therapy. Appropriate preventive strategies like influenza vaccination also need to be employed routinely.

KEY WORDS: Chronic obstructive pulmonary disease, exacerbation, influenza, viruses

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INTRODUCTION

Chronic obstructive pulmonary disease (COPD), a disorder of chronic airflow limitation (chronic airflow obstruction) not reversed by bronchodilators, is now the 3rd commonest cause of death worldwide. While most of the information on COPD prevalence, morbidity, and mortality is available from high-income countries, it is known that low- and middle-income countries already shoulder much of the burden of COPD with almost 90% of COPD deaths taking place in these countries.[1] Spirometrically documented COPD is common in Kashmir, the northern Indian state of Jammu and Kashmir, with a prevalence of about 19% among males and 14% among females above the age of 40 years;[2] much higher than reported previously on the basis of questionnaire surveys.[3]

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The natural history of COPD is punctuated by exacerbations that lead to considerable morbidity, mortality and an inexorable decline in pulmonary function. Exacerbations of COPD form one of the most common medical admissions, especially during winter when respiratory viral infections are common. Exacerbations are regarded to be infective in most cases, and viruses are believed to be a common cause of exacerbations. We have recently reported that influenza A and B viruses are associated with about 8% of COPD exacerbations.[4] Data regarding the contribution of other respiratory viruses in the causation of exacerbations of COPD are scant, especially from the developing countries. We herewith report our results of testing of patients for other respiratory viruses in patients with COPD exacerbation.

METHODS

A total of 233 consecutive consenting patients admitted with an exacerbation of COPD were enrolled from May 2011 to September 2012 for detection of respiratory viruses at a tertiary care facility in Srinagar, the summer capital of the Northern Indian state of Jammu and Kashmir. Kashmir has a temperate geography in contrast with the generally more tropical climate in the rest of the country, and we have earlier reported a temperate seasonality of influenza virus circulation[5,6] which contributes to the exacerbations of COPD in 8% cases.[4] Demographic and clinical parameters were recorded in each case. Twin nasopharyngeal/oropharyngeal swabs were collected from the patients as described earlier.[4] Tested for respiratory viruses including respiratory syncytial virus (RSV) A and B, parainfluenza (PIV) 1, 2, 3,[7] and 4,[8] human metapneumovirus (hMPV) A and B,[9] influenza A and B, enterovirus, corona NL65, OC43, and 229E viruses,[10] adenovirus 2 and 4,[11] rhinovirus,[10] and bocavirus,[12] were performed by in-house standardized duplex real time reverse-transcription polymerase chain reaction (qRT-PCR) using previously published primers and probes. The details of the enrollment and testing for influenza among these patients have been reported elsewhere.[4] Briefly, nasal and throat swabs were collected from participants at enrollment for testing by RT-PCR for influenza A and B viruses, and those positive for influenza A viruses were further subtyped for A/H1N1pdm09, A/H3N2, and seasonal H1N1 using US Centers for Disease Control and Prevention protocols.

The patients were managed with routine antibiotics, supportive oxygen therapy, noninvasive or invasive ventilation, and antiviral agents (oseltamivir) in case of influenza positivity. Antibiotics were withdrawn in ten patients in whom influenza viruses were detected and there was no other clinical or lab parameter suggestive of bacterial etiology such as purulence of sputum, polymorphonuclear leukocytosis, elevated C-reactive protein (CRP) or detection of bacteria on Gram's staining or culture; and the patients showed a consistent improvement. The patients were followed for about 30 days for any readmissions and at home mortality. The discharged patients were contacted telephonically for any mortality/readmission within 30 days. The results were analyzed employing SPSS 17.0 software (SPSS Inc. Released 2008. SPSS Statistics for Windows, Version 17.0. Chicago). The study was approved by the Institute Ethics Committee, and informed consent was obtained from all participants before recruitment.

RESULTS

The recruited patients included 152 male and 81 female patients with age ranging from 40 to 100 (median 65) years. The patients presented with respiratory symptoms of 3–8 days (median 5 days). The various symptoms experienced by the patients included cough (n = 229, 98%), worsening dyspnea (n = 226, 97%), wheezing (n = 214, 92%), increased sputum (n = 135, 58%), fever (n = 93, 40%) chills (n = 86, 37%), sore throat (n = 51, 22%), and nasal discharge (n = 44, 19%).

Hypertension (60.52%) and heart disease (14.16%) were the commonest comorbid illnesses. There were thirty current smokers; 50 (21.4%) reported second-hand tobacco exposure, and 50 (21.4%) reporting the use of biomass fuels (i.e., wood, crop build ups, or compost) for cooking/heating. Most (n = 213, 92%) of the participants used Kangri (personal heating devices consisting of earthenware pots carried along with live charcoal) or bukhari for personal heating. Seven patients had received influenza vaccine in the current season, and three were on chronic oral steroids whereas 72 were on home oxygen therapy.

Respiratory viruses were identified in nasal and throat swabs in 46 ((19.7%) of the 233 cases [Figure 1]. The various viruses detected are depicted in Table 1 and Figure 2. Influenza A/H3N2 and rhinoviruses were the commonest viruses detected. More than one virus was isolated in four cases consisting of hMPV-B + adeno-2 + inf-b; rhino + H3N2, PIV-1+ rhino; and PIV-1+ hMPV-B in one case each. Ancillary supportive therapeutic measures included antibiotics and steroids (n = 194, 83%). Antiviral therapy was instituted in influenza-positive patients. Noninvasive ventilation was used in 42 cases whereas invasive mechanical ventilation was needed in four cases. Three patients (1.3%) died in the hospital whereas one patient was readmitted within 30 days

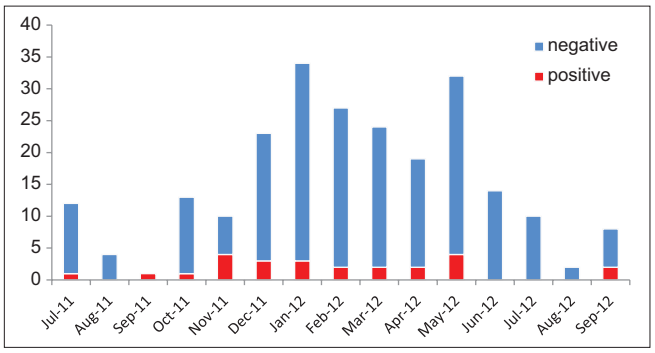

Figure 1: Monthly distribution of positive samples for respiratory viruses in acute exacerbation of chronic obstructive pulmonary disease patients

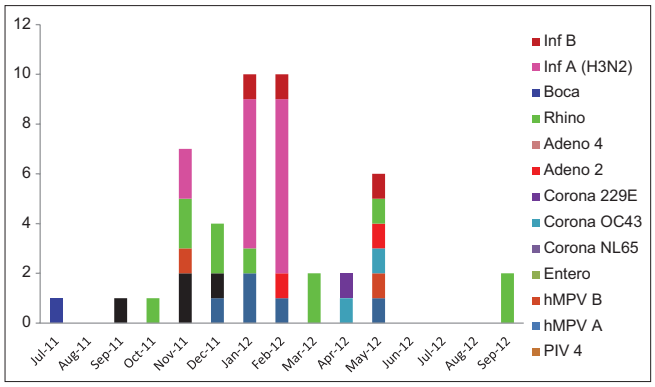

Figure 2: Monthly detection of the various viruses in patients with exacerbation of chronic obstructive pulmonary disease

Table 1: Various viruses detected among 233 patients with acute exacerbations of chronic obstructive pulmonary disease

Virus	*n* (%)
Influenza	18 (7.7)
Influenza A/H3N2	15 (83)
Influenza B	3 (17)
Rhinovirus	11 (4.7)
RSV A	5 (2.1)
PIV 1	4 (1.7)
hMPV B	2 (0.8)
Adenovirus 2	2 (0.8)
Corona virus OC43	2 (0.8)
Coronavirus 229E	1 (0.4)
Boca virus	1 (0.4)

RSV: Respiratory syncytial virus, PIV: Parainfluenza virus,hMPV:Human metapneumovirus

of discharge and another one died suddenly within 30 days of discharge at home. No autopsies were done, and all the patients who died had influenza A/H3N2 recovered from their nasopharyngeal specimens but antibiotics were not withdrawn in any of these. None of the patients who had other respiratory viruses had a readmission or died within 30 days of the hospital discharge.

DISCUSSION

Despite the increasing recognition that viruses are frequent in exacerbations of COPD (acute exacerbations of COPD [AECOPD]), it is less clear which viruses are involved and to what extent they contribute to exacerbations. Our data show that respiratory viruses are frequently associated with hospitalized patients with exacerbations of COPD, influenza, and rhinoviruses being the most common ones detected in the respiratory samples of the hospitalized patients. The detection rate of respiratory viruses in our study was similar to previous reports by Walsh *et al*.[13] However, McManus *et al*. reported a detection rate of 37% among their subjects with AECOPD.[14] In a recent meta-analysis of 17 eligible studies, weighted overall prevalence of respiratory viruses in patients with AECOPD was 39.3% compared to 13.6% in four studies in stable COPD, a pooled risk ratio for respiratory viral infection being 4.1 (95% confidence interval [CI]: 2.0–8.5) for AECOPD as compared with stable COPD, rhinovirus being the most common detected one. The results suggested that respiratory viruses probably are important etiological agents in patients with AECOPD as compared with the stable COPD patients.[15]

In this study, influenza and rhinoviruses were the commonest pathogens detected. In a recent systematic review of 19 studies involving 1728 patients with AECOPD, rhino/enteroviruses was found to be the most common (16.39%) pathogens involved followed by RSV (9.90%), influenza (7.83%) coronaviruses (4.08%), PIV (3.35%), adenovirus (2.07%), hMPV (2.78%), and bocaviruses (0.56%).[16] In the only study from India, Mohan *et al*. reported detection of viruses in 16 of the 137 patients with AECOPD and influenza was the most common virus detected (n = 11; 8%), followed by parainfluenza virus-1 (n = 3; 3.6%), RSV, and PIV3 (n = 1 each).[17] Three of the patients in our study who died had A/H3N2 influenza viral infection.

The detection rates of pathogens in AECOPD have been influenced by the diagnostic methods employed. Comprehensive RT-PCR has been regarded as a method of choice for detection of the viruses in the respiratory specimens.[18] Combining real-time PCR with conventional methods improves the ability to detect infectious etiologies of COPD exacerbations including both bacteria and respiratory viruses and may emerge as the standard of care in facilities with capacity to do the testing.[18] Recently microarray-based etiology of AECOPD pathogens was carried out in 200 patients with AECOPD. Human RSV (subtypes A and B) (40.5%), influenza virus (subtypes A, B, C) (11%), rhinovirus (8%) and human parainfluenza virus (subtypes A and B) (7.5%) were the commonest isolated strains.[19]

Most of the patients in this study were not vaccinated against influenza and pneumococcus despite clear recommendations for vaccination against these pathogens in patients with COPD. This trend of poor vaccination uptake is consistent with our previous report of poor uptake of influenza and pneumococcal vaccination in patients with COPD from low-income countries as compared to those from high-income countries.[20]

Since empirical utilization of antibiotics has prompted disturbing levels of antibiotic resistance, it would be very useful to distinguish between the viral and the bacterial etiology of AECOPD so that antibiotic use could be curtailed and properly rationalized. Antibiotic use in severe COPD exacerbations has been recommended routinely, even as there is a paucity of placebo-controlled clinical trials and up to today, no single study has been powered sufficiently to prove the efficacy of antibiotic treatment in AECOPD.[21] In a recent Cochrane review of 16 randomized controlled studies involving 2068 patients, the authors concluded that antibiotics for COPD exacerbations showed large and

consistent beneficial effects across outcomes of patients admitted to an intensive care unit. However, for outpatients and inpatients, the results were inconsistent. The risk for treatment failure was significantly reduced in both inpatients and outpatients when all trials (1957–2012) were included but not when the analysis for outpatients was restricted to currently used antibiotics. Furthermore, antibiotics had no statistically significant effect on mortality and length of hospital stay in inpatients and almost no data on patient-reported outcomes exist. These inconsistent effects call for research into clinical signs and biomarkers that help identify patients who benefit from antibiotics and patients who experience no effect, and in whom downsides of antibiotics (side effects, costs, and multi-resistance) could be avoided.[22] While some clinical and lab parameters have been suggested to distinguish between the two, in a recent study in which viruses were isolated from 22% of 72 enlisted patients of AECOPD, bacterial diseases could not be separated from viral disease by white cell number, CRP or procalcitonin levels.[23] However, the utility of these parameters needs to be probed further, and there is a distinct need for a biomarker for distinguishing the bacterial from a viral infection. An extensive placebo-controlled study is underway in Germany to assess if anti-microbial treatment is at all needed in COPD exacerbations.[21]

In ten of our patients in whom influenza viruses returned positive on testing, there was absence of evidence of a bacterial infection, we used oseltamivir as stand-alone medication without any complications. All the three patients who died had H3N2 detected in them, and this could argue in favor of starting antiviral medication in patients with AECOPD, pending a result of the respiratory specimen, when a patient of AECOPD presents with features of influenza-like illness or a severe acute respiratory infection during a time of heightened activity of influenza circulation. According to the Advisory Committee on Immunization Practices, antiviral treatment is recommended as soon as possible for patients with confirmed or suspected influenza who have a severe, complicated, or progressive illness or who require hospitalization.[24] Antiviral treatment for influenza is recommended especially for patients who are at a higher risk for influenza-associated complications and chronic pulmonary disease for one such group. De-escalation to antivirals alone might be justified if the testing of the respiratory specimens returns positive for influenza. However, this approach would require further study on sufficiently powered patient groups.

CONCLUSIONS

Viral infections seem to contribute to the exacerbations of COPD in our settings and should be strongly considered in the management of such patients. Further studies reproducing our data from other areas could perhaps help reduce the inappropriate empiric use of antibiotics in the event of an influenza viral exacerbations. Our data also strongly advocate strenghtening the routine use of influenza vaccination in patients with COPD.

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Conflicts of interest

There are no conflicts of interest.

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