Journal of Clinical Virology 61 (2014) 181–188

Contents lists available at ScienceDirect

Journal of Clinical Virology

journal homepage: www.elsevier.com/locate/jcv

Review

The relevance of respiratory viral infections in the exacerbations of chronic obstructive pulmonary disease—A systematic review

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ARTICLE INFO

Article history:
Received 30 March 2014
Received in revised form 16 June 2014
Accepted 25 June 2014

Keywords:
Pulmonary disease, chronic obstructive
Exacerbation
Viruses
Polymerase chain reaction
Systematic review

ABSTRACT

Background: Despite the increasing knowledge on the role of viruses in exacerbations of COPD (AECOPD), it is less clear which viruses are involved and to what extent they contribute to exacerbations. This review aims to systematically combine and evaluate the available literature of the prevalence of respiratory viruses in patients with AECOPD, detected by PCR.
Methods: An electronic search strategy was performed on PubMed and Embase and reference lists were screened for eligible studies. Cross-sectional, prospective studies and case-control studies were included. The primary outcome measure was the prevalence of respiratory viruses (adenovirus, bocavirus, coronavirus, EBV, hMPV, influenza, parainfluenza, rhino-/enterovirus, RSV) in respiratory secretions of patients during an AECOPD. Secondary outcomes were the odds of the presence of the viruses in different respiratory secretions and the odds of the presence of viruses in upper and lower respiratory tract (URT/LRT) samples.
Results: Nineteen studies with 1728 patients were included. Rhino-/enteroviruses (16.39%), RSV (9.90%) and influenza (7.83%) were the most prevalent viruses detected with lower detection rates of coronaviruses (4.08%) and parainfluenza (3.35%). Adenovirus (2.07%), hMPV (2.78%) and bocaviruses (0.56%) appear to be rare causative agents of AECOPD. Definitive conclusions regarding the role of EBV cannot be made. Seven of the eight analyzed viruses had a higher prevalence in LRT samples. Coronaviruses were detected more frequently in the URT.
Conclusions: Respiratory viruses are frequently detected in both URT and LRT samples in AECOPD with rhino-/enteroviruses, RSV and influenza viruses the most prevalent viruses. Detection rates vary between the two sites for different viruses.

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Abbreviations: AECOPD, acute exacerbation of chronic obstructive pulmonary disease; COPD, chronic obstructive pulmonary disease; EBV, Epstein–Barr virus; ECHO, enteric cytopathogenic human orphan; FEV1, forced expiratory volume in one second; hMPV, human metapneumovirus; ICTV, International Committee on Taxonomy of Viruses; LRT, lower respiratory tract; PCR, polymerase chain reaction; qRT-PCR, quantitative quantitative real time-polymerase chain reaction; QUADAS, quality assessment of diagnostic accuracy studies; RSV, respiratory syncytial virus; RT-PCR, reverse transcriptase-polymerase chain reaction; URT, upper respiratory tract.

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http://dx.doi.org/10.1016/j.jcv.2014.06.025
1386-6532/

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1. Introduction

Chronic obstructive pulmonary disease (COPD) is characterized by persistent airflow obstruction with the most important risk factor for the development of COPD being exposure to cigarette smoke. The course of the disease is progressive and punctuated by the occurrence of exacerbations that can accelerate lung function decline and increase mortality [1,2]. The global initiative for chronic obstructive lung disease (GOLD) classification defines an exacerbation as "an acute event characterized by a worsening of the patient's respiratory symptoms that is beyond normal day-to-day variations and leads to a change in medication" [3]. Mortality in COPD increases with the number of exacerbations [2] and exacerbations often lead to hospitalization with high treatment costs [1]. Therefore, prevention and optimal management is of high importance. Acute exacerbations are frequently triggered by respiratory tract infections [3]. Respiratory viruses are frequently detected in COPD exacerbations [4], but their role in the pathogenesis remains unclear [5]. The first studies investigating a possible causal role of viruses in COPD exacerbations identified respiratory viruses by serology and viral culture; however, detection rates were generally low. More recently, more sensitive and specific diagnostic methods have become available for detection of respiratory viruses utilizing PCR and its derived forms [6]. Despite the increasing knowledge on the role of viruses in exacerbations of COPD, it is less clear which viruses are involved and to what extent they contribute to exacerbations. The prevalence of viral infection detected by PCR in COPD exacerbations has been reviewed systematically by Mohan [7]. The review demonstrated the relatively high prevalence of picornaviruses and influenza viruses in COPD exacerbations [7]; however, only eight studies were included. In order to further investigate the role of respiratory viral infections in COPD exacerbations on the basis of more recent studies, the present review systematically evaluates additional publications based on an extended selection of articles, selected by a more systematic search strategy. Beside the pooled prevalences of the respiratory viruses, detection in the upper respiratory tract (URT) or the lower respiratory tract (LRT) are also evaluated.

2. Methods

2.1. Protocol and registration

This systematic review was written according to the guidelines of the PRISMA statement for reporting systematic reviews [8].

2.2. Eligibility criteria

2.2.1. Studies and patients

Cross-sectional, prospective studies and case-control studies were included provided the main aim was to determine the prevalence of respiratory virus(es) in COPD exacerbations. The full, original paper of the study or a letter had to be available. Other studies with retrospective inclusion of patients (i.e. sample-related or laboratory-based studies) and studies in an intensive care setting were not included. Intensive care patients represent a distinct group because of significant changes in oropharyngeal flora, hence studies involving these patients were not evaluated in this review. All patients included were diagnosed with COPD by lung function measurements and were evaluated at the time of exacerbation. Patients with asthma or immunosuppressed patients were excluded.

2.2.2. Types of outcome measures

The primary outcome measure was the prevalence of (one or more) respiratory viruses (adenovirus, bocavirus, coronavirus, Epstein–Barr virus (EBV), human metapneumovirus (hMPV), influenza, parainfluenza, rhino-/enterovirus, and respiratory syncytial virus (RSV)) in respiratory secretions of patients during an exacerbation of COPD. Nosocomial infections (hospitalization within the last four weeks or collection of samples later than 48 h after hospitalization) were excluded. Secondary outcomes were the odds of the presence of the viruses in several respiratory secretions and the odds of the presence of viruses in URT and LRT samples.

2.3. Information sources

The publications used for this systematic review were obtained by a full electronic search strategy using the search engine on the databases PubMed and Embase, last performed on May 10th 2014. The resulting manuscripts were carefully analyzed and included when meeting the eligibility criteria by two authors (WZ, PM). Subsequently, the reference lists of the selected articles were screened to ensure no relevant papers were missed.

2.4. Search

The described search strategy was performed by using the following syntax in PubMed:

(((((((“Pulmonary Disease, Chronic Obstructive”[Mesh])) AND (“Disease Progression”[Mesh]))) OR (((copd)) AND (exacerbation)))) AND ((((“Viruses”[Mesh])) OR (respiratory viral