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Pathogen profiles and molecular epidemiology of respiratory viruses in Japanese inpatients with community-acquired pneumonia

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ABSTRACT

Background: The etiological profile of viruses among adult patients with community-acquired pneumonia (CAP) has not been characterized yet. The aim of this study was twofold: first, investigate the pathogen profiles and the molecular epidemiology of respiratory viruses among Japanese CAP patients; and second, explore the clinical significance of viral infections.
Methods: A cross-sectional observational study was conducted at Kyorin University Hospital. To identify respiratory pathogens, hospitalized CAP patients were enrolled, and reverse transcriptase–polymerase chain reaction technology was applied alongside conventional microbiological methods. Phylogenetic and pairwise distance analyses of 10 viruses were performed. CAP patients were divided into four etiological groups (virus alone, bacteria alone, co-detection of virus and bacteria, and not detected) and the clinical findings were compared.
Results: Seventy-six patients were enrolled. Bacteria alone were detected in 39.5% ($n=30$) of CAP patients. Virus alone or co-detection were found in 10.5% ($n=8$) and 11.8% ($n=9$) of cases, respectively. *Streptococcus pneumoniae* and human metapneumovirus were the most frequently detected bacterium and virus, respectively. Phylogenetic analyses of human metapneumovirus, human rhinovirus, and human respiratory syncytial virus showed that different subgroups and genotypes might be associated with CAP. Respiratory failure was more common when a virus was detected (both virus alone and co-detection groups; $n=17$, 100%, $p<0.05$) than when a bacteria alone was detected ($n=17$, 56.7%).
Conclusion: Prevalence of respiratory virus infection in CAP inpatients was 22.3%. The detected viruses display high genetic divergence and correlate with increased respiratory failure.

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1. Introduction

Community-acquired pneumonia (CAP) is a life-threatening respiratory disease of worldwide importance [1]. According to several studies from developed countries, the annual incidence of CAP in adults is in the range of 0.5–1.1%, and the mortality rate of hospitalized CAP patients is 4–14% [2]. Previous reports have suggested that various pathogens including bacteria, fungi, and viruses are associated with CAP [3]. Among these, *Streptococcus pneumoniae* (pneumococcus) is a major cause of CAP in adult patients, particularly in those with severe diseases [2–5]. Bacteria such as *Haemophilus influenzae*, methicillin-sensitive *Staphylococcus aureus* (MSSA), *Legionella pneumophila*, and *Moraxella catarrhalis* are associated with CAP in adult inpatients [2–5], while other types such as *Mycoplasma pneumoniae* are detected in relatively mild CAP in outpatients [6].

Until recently, respiratory viruses such as human respiratory syncytial virus (RSV), human rhinovirus (HRV), human parainfluenza virus (HPIV), and human metapneumovirus (HMPV) have been mainly associated with lower respiratory tract infections (LRTI) including bronchitis, bronchiolitis, and pneumonia in children [7–9].

Respiratory viruses such as RSV, HRV, HMPV, and adenovirus are present in two-thirds of children with CAP [10].

Apart from causing LRTI, these viruses can exacerbate asthma and chronic obstructive pulmonary disease (COPD) [11–14]. For example, Dowell et al. showed that RSV was associated with 4.4% of adult cases of LRTI during winter [15]. Recent molecular epidemiological studies suggest that these viruses can be classified into numerous phylogenetic subtypes and genotypes. Specifically, there are over 150 genotypes of HRV species A to C (HRV-A to -C). Similarly, RSV and HPIV species can be subclassified into several genotypes. Recent studies have demonstrated the presence of these respiratory viruses and/or bacteria in adult patients with CAP [16,17]. However, the molecular epidemiology in adult CAP Japanese patients is poorly understood.

We conducted pathogen profiling and phylogenetic analyses of various respiratory viruses detected in hospitalized CAP patients in Japan and characterized these patients in terms of infectious viral and/or bacterial pathogens.

2. Patients and methods

2.1. Patients and study design

In this cross-sectional observational study, we recruited consecutive patients admitted to Kyorin University Hospital (Tokyo, Japan) between August 2012 and August 2014 with a diagnosis of CAP. Pneumonia was defined as the presence of new infiltrates on chest X-rays along with other suggestive signs and symptoms: cough, sputa, fever, chills, dyspnea, pleuritic chest pain, disturbance of consciousness, and crackles. Exclusion criteria included the following: (a) residence in a long-term nursing home or healthcare home; (b) hospitalization within the preceding 90 days; (c) elderly persons or physically disabled persons who needed healthcare; (d) continuous endovascular therapy (i.e., hemodialysis, anti-cancer, or immunosuppressive drugs); (e) onset of pneumonia 48 h after admission; and (f) active tuberculosis.

2.2. Clinical data collection

The following data were recorded on admission: age, sex, comorbid illnesses (chronic heart diseases, COPD, asthma, other lung diseases, diabetes mellitus, or active cancer), immunodeficiency status (i.e., use of immunosuppressive drugs or prednisolone dose of ≥ 5 mg/day, and HIV-positive patients), use of anti-microbial drugs (anti-bacterial or anti-influenza) before admission, and clinical or laboratory findings. Respiratory failure was defined as PaO_2 <60 mmHg or SpO_2 <90% in room air. In patients who underwent home oxygen therapy, respiratory failure was diagnosed at the point when further oxygen supply was needed to maintain the patient's previous condition.

The severity of pneumonia was assessed using the pneumonia severity index (PSI), a prediction rule with points assigned based on age, coexisting diseases, and abnormal physical findings. PSI stratifies CAP patients into five classes (I–V) to predict their risk of mortality [18]. Severe pneumonia is defined as PSI class IV or V. Follow-up variables included the need for mechanical ventilation (invasive and non-invasive) within 5 days of admission, and mortality within 30 days.

2.3. Samples

Samples collected on admission included sputum, nasopharyngeal swab (NPS), bronchoalveolar lavage fluid (BALF), blood, and urine. Serological tests for *Mycoplasma pneumoniae* were performed on admission and after several weeks, when possible. Invasive diagnostic methods were conducted according to clinical judgment. Respiratory samples for PCR-based detection of respiratory viruses, *Mycoplasma pneumoniae*, and *Chlamydophila pneumoniae* were collected separately from those

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