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Original article

Distribution and annual changes in *Streptococcus pneumoniae* serotypes in adult Japanese patients with pneumonia

Kentaro Akata [a], Bin Chang [b], Kazuhiro Yatera [a, *], Toshinori Kawanami [a], Kei Yamasaki [a], Keisuke Naito [a], Shingo Noguchi [a], Hiroshi Ishimoto [a], Hiroshi Mukae [a]

[a] Department of Respiratory Medicine, School of Medicine, University of Occupational and Environmental Health, Japan, Kitakyushu, Japan
[b] Department of Bacteriology I, National Institute of Infectious Diseases, Tokyo, Japan

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ABSTRACT

Background: *Streptococcus pneumoniae* is one of the main causative bacteria in patients with pneumonia; however, there are no data regarding serotype changes in adult patients with pneumonia after the introduction of the pneumococcal vaccine (PCV7) for childhood immunization in Japan. We herein evaluated the serotype distribution in adult patients with pneumonia.

Methods: This retrospective epidemiological study was performed at the University of Occupational and Environmental Health, Japan from January 2011 to December 2013. The serotypes of pneumococcal isolates obtained from patients with pneumonia were evaluated along with the patients' clinical information.

Results: A total of 81 patients with pneumococcal pneumonia (89 episodes) from whom *S. pneumoniae* was isolated were included. The numbers (percentages) of sample types were as follows: sputum 55 (61.8%), intratracheal tube suction 15 (16.9%), intrabronchial sampling 5 (5.6%) and bronchoalveolar lavage fluid 14 (15.7%). The PCV7 serotypes decreased significantly among the patients with pneumococcal pneumonia from 46.4% in 2011 to 20.0% in 2013 ($p < 0.05$). Conversely, PCV13 and 23-valent pneumococcal polysaccharide vaccination (PPSV23) serotypes other than PCV7 serotypes mildly increased during this period. In addition, the frequency of serotypes 19F, 23F and 4 (which are covered by PCV7) decreased annually; however, the changes in the frequencies of the other serotypes were not significant.

Discussion: This study demonstrated the yearly decrease of PCV7 serotypes in adult pneumococcal pneumonia patients after introducing PCV7 into the childhood immunization schedule in Japan. Continued surveillance of pneumococcal serotype changes is important for the proper use of different pneumococcal vaccines.

1. Introduction

PCV7 was introduced in 2000 and made available for routine use in all children 2–23 months of age and children 24–59 months of age at risk for pneumococcal infection in the United States [1]. Subsequent surveillance studies demonstrated a marked decrease in the prevalence of pneumococcal infection caused by vaccine serotypes [2,3], and similar changes in replacement from vaccine serotypes to non-vaccine serotypes have been observed in other countries [4–6]. A reduced incidence of invasive pneumococcal disease (IPD) caused by PCV7 serotypes among unvaccinated patients of all ages, including the elderly, after routine childhood PCV7 vaccination has also been reported [2,7–9], probably due to herd transmission of pneumococcal serotypes from children to adults.

PCV7 was first introduced in October 2009 in Japan, and its clinical use in infants on a voluntary basis was introduced in February 2010. The Japanese official program of the Provisional Special Fund for the Urgent Promotion of Vaccination promoted the vaccination of PCV7 for children <5 years of age in November 2010; as a result, the estimated rate of PCV7 vaccination for these children

* Corresponding author. Department of Respiratory Medicine, University of Occupational and Environmental Health, Japan, 1-1 Iseigaoka, Yahatanishiku, Kitakyushu city, Fukuoka 807-8555, Japan. Tel.: +81 93 691 7453; fax: +81 93 602 9373.
E-mail address: yatera@med.uoeh-u.ac.jp (K. Yatera).

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drastically increased annually from <10% in 2010 to 50–60% in 2011 and 80–90% in 2012. Consequently, the prevalence of PCV7 serotypes in patients with IPD rapidly decreased from 73.3% in 2010 to 54.8% in 2011 and 14.7% in 2012. Conversely, the prevalence of non-PCV7 serotypes has significantly increased during these three years ($p < 0.001$) [10]. Similar to the observed changes in the prevalence of pneumococcal serotypes in adults after the introduction of PCV7 in children in the United States, a decrease of PCV7 serotypes in adults after starting PCV7 childhood vaccination in Japan is also speculated. However, there are no data regarding serotype changes after the introduction of pneumococcal vaccines in Japan to date. Therefore, we herein evaluated the yearly changes in the vaccine serotypes of pneumococci in adult patients with pneumonia.

2. Patients and methods

In this retrospective epidemiological study, *Streptococcus pneumoniae* was isolated from 81 patients (89 episodes) with pneumococcal pneumonia. These patients were enrolled at the university hospital of the University of Occupational and Environmental Health, Japan from January 2011 to December 2013. The following patient information was evaluated: age, gender, sample site, type of pneumonia, presence of IPD, history of PPSV23, body mass index (BMI), smoking history, Eastern Cooperative Oncology Group (ECOG) performance status (PS) of premorbid condition, comorbid diseases, clinical manifestations and laboratory findings, including urinary antigen tests for *S. pneumoniae* (BinaxNow® *S. pneumoniae*, Binax, Portland, ME, USA), radiological findings of pulmonary infiltration on chest X-rays and computed tomography (CT), the pneumonia severity index (PSI) and mortality. The vaccination history of PPSV23 was directly confirmed by the patient. The PSI is usually used to evaluate the severity of pneumonia prior to admission; however, it was used for descriptive purposes in this study. This study was conducted in accordance with the Helsinki Declaration and approved by the Human and Animal Ethics Review Committee of the University of Occupational and Environmental Health, Japan (No. 26-226). Individual informed consent was not required by the Ethical Board as this study was retrospective and all personal data were handled under strict security and the results were de-identified.

2.1. Diagnostic criteria for community-acquired pneumonia (CAP), healthcare-associated pneumonia (HCAP) and hospital-acquired pneumonia (HAP)

All patients exhibited the presence of new areas of infiltration on chest radiographs and new clinical findings including at least two of the following: fever, sputum production, cough and leukocytosis (white blood cell count ≥10,000/μl).

The definitions of CAP, HCAP and HAP were as follows. CAP was defined as an acute infection of the pulmonary parenchyma associated with at least some symptoms of acute infection (e.g., fever, cough, sputum production and/or dyspnea) accompanied by the presence of an acute infiltrate on a chest radiograph or auscultatory findings consistent with pneumonia [11]. HCAP was also defined according to the ATS/IDSA guidelines [12] including at least one of the following criteria [1]: hospitalization for two days or more within the preceding 90 days [2]; residence in a nursing home or extended care facility [3]; home infusion therapy (including antibiotics); and [4] chronic dialysis within 30 days. HAP was defined as pneumonia occurring 48 h or more after admission and not incubating at the time of admission [13,14].

The criteria for aspiration risk factors defined by Marik et al. [15] were used in this study, and patients with 1) neurologic dysphagia, 2) disruption of the gastroesophageal junction (including gastroesophageal disorders) or 3) anatomical abnormalities of the upper aerodigestive tract were thought to be at risk for aspiration.

2.2. Identification of bacteria, antimicrobial susceptibility testing and serotyping

Bacterial cultures and identification and antimicrobial susceptibility tests were performed, and the minimum inhibitory concentrations (MICs) were determined using the agar dilution method according to the guidelines of the National Committee for Clinical Laboratory Standards [16]. The isolates were classified as penicillin-sensitive *S. pneumoniae* (PSSP) when the MIC was ≤2 μg/ml or penicillin-resistant *S. pneumoniae* (PRSP) when the MIC was ≥8 μg/ml. Similarly, pneumococci were considered to be sensitive and resistant to clarithromycin (CAM) when the MIC of CAM was ≤0.25 and ≥1, respectively, and sensitive and resistant for levofloxacin (LVFX) when the MIC was ≤2 and ≥8, respectively. Serotyping was performed with the Quellung reaction using antisera from Statens Serum Institute (SSI; Copenhagen, Denmark) [17]. Shortly, a mixture of cultured *S. pneumoniae*, sera and methylene blue was applied on the slide glasses, and the serological types were determined to clarify the capsular swelling reaction using light microscopy.

2.3. Statistical analysis

The SPSS software package (version 19) was used for the statistical analyses. Fisher's exact test for tables (2 × 2) and the Mann–Whitney (non-parametric) test were used as appropriate. A p value of <0.05 was considered to be statistically significant.

3. Results

3.1. Patient characteristics

The background characteristics of the patients with pneumonia are shown in Table 1. The average age was 66.7 ± 13.8 years, 65.2% of the subjects were male and the average BMI was 20.4 ± 4.2. Fifty-five *S. pneumoniae* isolates were collected from patient sputum (61.8%), 15 (16.9%) were collected via intratracheal tube suction, five (5.6%) were collected via intrabronchial sampling and 14 (15.7%) were collected from BALF. The percentages (numbers) of patients with CAP/HCAP/HAP/IPD were 53.9%/16.9%/29.2%/5.6% (48/15/26/5), respectively. Eleven (12.4%) patients had a history of PPSV23 vaccination, while 72 (80.9%) had not received previous vaccinations; the status of six (6.7%) patients was unknown. The percentages (numbers) of patients with ECOG-PS of premorbid condition 0, 1/2/3, 4 were 58.4%/13.5%/28.1% (52/12/25), respectively, and 25/89 (28.1%) patients had chronic respiratory diseases. The proportion of patients who received glucocorticoids (prednisolone; PSL ≥5 mg/day) or immunosuppressive agents was 19.1% (17/89) and 15.7% (14/89), respectively. The clinical and laboratory data, PSI, mortality and drug resistant data are shown in Table 2. The percentage of patients with orientation disturbance was 18.0% (16/89) and the average serum level of albumin (g/dl) was 3.11 ± 0.56. The proportions of patients with positive/negative urinary antigen tests for *S. pneumoniae* were 29.2%/27.0% (26/24), while the results were unknown for 43.8% (39) of the patients. The percentage of patients with gravity-dependent opacity on chest CT was 77.8% (56/89) and the average PSI score was 96.8 ± 41.5. The in-hospital and 30-d mortalities were 10 (11.8%) and 5 (5.5%), respectively. According to the antibiotic susceptibility testing, the numbers of cases of PRSP and macrolide- and quinolone-resistant pneumococci were 0 (0%), 74 (83.1%) and 1 (1.1%), respectively.