Vaccine xxx (2014) xxx–xxx

Contents lists available at ScienceDirect

Vaccine

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

Effects of 7-valent pneumococcal conjugate 1 vaccine on the severity of adult 2 bacteremic pneumococcal pneumonia

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ARTICLE INFO

Article history:
Received 3 December 2013
Received in revised form 4 April 2014
Accepted 24 April 2014
Available online xxx

Keywords:
Pneumococcal vaccination
Severity of disease
Pneumococcal serotypes
Bacteremic pneumococcal pneumonia

ABSTRACT

Purpose: The introduction of a 7-valent conjugate pneumococcal vaccine (PCV7) in children largely affected the prevalence of adult pneumococcal pneumonia. In this study we investigated whether the clinical severity of adult bacteremic pneumococcal pneumonia has also altered following the introduction of pediatric PCV7 vaccination.
Methods: Adults hospitalized with bacteremic pneumococcal pneumonia between 2001 and June 2011 at two Dutch hospitals were included retrospectively. Clinical data on patient characteristics, comorbidities and severity of disease were obtained and pneumococcal serotypes were determined.
Results: Among 343 patients investigated, those infected with PCV7 serotypes had a higher PSI score ($p = 0.0072$) and mortality rate ($p = 0.0083$) compared with the remainder of the cohort. Since the introduction of PCV7 the proportion of pneumococcal pneumonias caused by serotypes 1 and 7F (p-values 0.037 and 0.025) increased, as well as the rate of pleural effusion and empyema (p-values 0.011 and 0.049). Whilst de proportion of adults infected with PCV7 serotypes decreased after the introduction of PCV7 ($p = 0.015$), PSI scores in these patients remained higher ($p = 0.030$), although mortality rates between PCV7 and non PCV7 types equalized. After the introduction of PCV7 a marked shortening in hospital stay was observed only among patients infected with non PCV7 serotypes ($p = 0.019$).
Conclusions: After pediatric PCV7 vaccination, adult bacteremic pneumococcal pneumonia was more frequently caused by serotype 1 or 7F and pleural effusion occurred more often. Although PSI scores remained higher among adults infected with PCV7 serotypes, mortality rates equalized between PCV7 and non PCV7 types alongside shortening of hospital stay in patients infected with PCV7 serotypes.

1. Introduction

Streptococcus pneumoniae is the most common cause of community acquired pneumonia worldwide. Twenty-four percent of pneumococcal pneumonia cases are accompanied by bacteremia, as detected by blood culture [1]. The clinical severity of a bacteremic pneumococcal pneumonia can vary from mild respiratory disease to septic shock or even death [2]. This wide spectrum of clinical severity is caused by differences in both pathogen and host characteristics, and their behavior during infection and therapy.

All pneumococci cultured from blood are veiled by a dense polysaccharide capsule that facilitates immune evasion and enables survival. Indeed only an appropriate immune response directed against the capsule is known to result in clearance of the pneumococcus from the circulation, as illustrated by effective polysaccharide vaccination [3]. However, over 93 different polysaccharide capsule structures, denominated as serotypes, are known to date and only a limited number are included in the current vaccines. The selection of serotypes included in the 7-, 10-, and 13-valent pneumococcal conjugate vaccines (PCVs) is based upon the frequency with which these serotypes caused invasive pneumococcal disease (IPD) prior to conjugate vaccine introduction, with the aim to maximally reduce the frequency of pneumococcal disease. Although the introduction of the pneumococcal conjugate vaccines in national vaccination schemes has reduced the incidence of pneumococcal disease caused by the vaccine serotypes [3], non-vaccine

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http://dx.doi.org/10.1016/j.vaccine.2014.04.089
0264-410X/

serotypes are increasingly being isolated from both pediatric and adult patients with IPD [4–6]. Also in The Netherlands serotype replacement has been observed following the introduction of PCV7 in the National Pediatric Vaccination Program in 2006 [7].

The primary objective of pneumococcal vaccination is to reduce morbidity and mortality due to IPD. The replacement of vaccine serotypes by other serotypes upon vaccination has on one hand impaired the anticipated reduction in IPD frequency, but may also entail changes in the clinical severity of pneumococcal pneumonias post PCV7. It has for example been shown that mortality from pneumococcal pneumonia is related to the infecting serotype [8–12]. Moreover, if circulation of specific serotypes in the population is suppressed by vaccination, this may even influence serotype specific disease characteristics as we know them. Therefore, monitoring of both disease frequency and severity after introduction of a pneumococcal vaccine are important to guide further vaccine development. In addition to mortality, disease severity can also be measured by more subtle clinical parameters and the required intensity of treatment.

In this study the clinical severity of adult bacteremic pneumococcal pneumonia after the introduction of PCV7 vaccination in children was investigated.

2. Methods

2.1. Study population

Between January 2000 and June 2011, all adults admitted to two Dutch hospitals with a first episode of bacteremic pneumococcal pneumonia were retrospectively included in this study according to their hospital medical records. This observational cohort study was approved by the Local Medical Ethics Committees of both participating hospitals.

2.2. Clinical parameters

The following cohort characteristics were extracted from hospital medical records: age, gender, comorbidities (also expressed in Charlson comorbidity score), pneumococcal vaccination status and duration of symptoms before admission. To estimate severity of disease at admission, data on both the absolute Pneumonia Severity Index (PSI) score as well as the PSI risk class were collected, in addition to the presence of pleural effusion, pleural empyema, and systemic inflammatory response syndrome (SIRS). The PSI is a clinical prediction rule that assesses severity of disease at admission and enables stratification to risk classes which predict mortality rate. The index is based on 20 patient characteristics which cover demographic factors, findings on physical examination and laboratory and radiographic findings [13]. An adequate PSI score was defined to be based on $\geq$16 patient characteristics. Other parameters to assess morbidity were based on required intensity of treatment: admission to an intensive care unit (ICU), mechanical ventilation, and hospital stay among survivors. Clinical outcome was evaluated by in-hospital mortality, 30-day mortality, and time to death.

2.3. Pneumococcal strains

Pneumococcal strains isolated from blood cultures were stored in skim milk glycerol 10% at −80 °C. A Columbia agar plate with 5% sheep blood (Beckton Dickinson BV, Breda, The Netherlands) was inoculated with the pneumococcal isolate and incubated for 24 h at 37 °C and 5% CO_2. Twenty to thirty colonies of the pneumococcal isolate were picked from the blood agar plate and transferred into 5 ml of Todd Hewitt broth (Merck, Darmstadt, Germany) with 5% yeast extract or M17 broth (Merck) with 0.5% glucose and incubated at 37 °C and 5% CO_2 until slight turbidity (mid log phase) was reached. The liquid culture was centrifuged at 4 °C at 3000 × *g* for 10 min and the produced bacterial pellet was washed with 1 ml PBS and stored at −20 °C. DNA was isolated using the DNeasy Blood and Tissue Kit (Qiagen, Venlo, The Netherlands) according to the manufacturer's protocol for DNA isolation from Gram positive bacteria. Multiplex PCR analysis was performed according to Pai et al. [14]. In case multiplex PCR was inconclusive, serotyping was performed by Quellung using Pneumococcus Neufeld Antisera (Statens Serum Institut, Copenhagen, Denmark) according to the manufacturer's instructions.

2.4. Statistical analysis

The correlation between the predicted and actual mortality rates per PSI risk class was tested by a Spearman rank test. The PSI score was normally distributed (Shapiro–Wilk test $p = 0.081$) and homoscedasticity was met for variance in PSI scores among patient groups infected with different serotypes (Levene statistic $p = 0.43$). To explore whether differences in mean PSI scores could be expected between groups of patients infected with particular serotypes a one-way analysis of variance (ANOVA) was applied. Differences in disease severity parameters caused by specific serotypes were statistically tested by an unpaired *t*-test for normally distributed continuous variables, a Mann–Whitney *U* test for not normally distributed continuous variables and a Chi-square test (Fisher's exact test if <10 cases in a cell) for dichotomous variables. The significance level was set at 0.05, and *p*-values for differences in PSI score were corrected for multiple testing by the Benjamini–Hochberg False Discovery Rate procedure [15].

3. Results

3.1. Study population

Three hundred and forty-three adult bacteremic pneumococcal pneumonia patients were included in the study. The median age (IQR) was 70 years (56–80). At the time of infection, none of the patients had received previous pneumococcal vaccination. The overall in-hospital mortality was 13.5% (45 out of 334) and survivors' median hospital stay (IQR) was 11 days (7–16). An adequate PSI score was obtained for 294 of the 343 patients (86%). Of the bacteremic pneumococcal pneumonia patients, 3.1% fell into PSI risk class I, 17.3% in class II, 17.3% in class III, 38.1% in class IV, and 24.1% in class V. The actual 30-day mortality within the PSI risk classes correlated with the predicted risk of mortality (Spearman $r = 0.9747$, $p = 0.017$). The causative serotype was determined in 330 of the 343 patients. Thirty-one different serotypes were observed within the cohort. The mean ± SD PSI score among the cohort was 103.3 ± 38.1. One-way ANOVA suggested the existence of differences in PSI scores between groups of patients infected with particular serotypes in the cohort ($p = 0.00014$), The distribution of the PSI score over the different serotypes is shown in Fig. 1. Patients infected with either serotype 1 or serotype 7F had a significantly lower PSI score and risk class, compared to the remainder of the cohort (FDR corrected *p*-values 0.00068 and 0.0056, respectively). Furthermore, the patients infected with PCV7 serotypes had significantly higher PSI scores, compared to patients infected with other serotypes ($p = 0.0072$). The serotypes that contributed most to total mortality were serotype 3, 8, 4 and 14. A high mortality rate was observed among patients infected with serotype 6A (44.4%). In contrast, all of the 35 patients infected with serotype 1 and 94.1% (32 out of 34) of patients infected with serotype 7F survived.

Please cite this article in press as: Cremers AJH, et al. Effects of 7-valent pneumococcal conjugate 1 vaccine on the severity of adult 2 bacteremic pneumococcal pneumonia. Vaccine (2014), http://dx.doi.org/10.1016/j.vaccine.2014.04.089