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ORIGINAL ARTICLE

Comparison of invasive pneumococcal disease caused by serotype 19A and non-19A pneumococci in children: More empyema in serotype 19A invasive pneumococcal disease



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KEYWORDS

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Objective: To delineate whether serotype 19A invasive pneumococcal disease (IPD) comprised significantly more necrotizing pneumonia and empyema in children, we compared the clinical characteristics between serotype 19A and non-19A IPD.

Methods: Between January 2007 and December 2011, cases of children with IPD who were treated at the National Taiwan University Hospital were reviewed. Patients were assigned to the 19A group or the non-19A group based on the serotype. Their demographic data, clinical course, laboratory results, diagnosis, complications, and sequelae were collected and analyzed.

Results: Overall, 27 patients were included in the 19A group and 29 patients in the non-19A group. Compared with non-19A group, serotype 19A tended to cause IPD in patients without major underlying diseases ($p = 0.015$). Bacteremia without pneumonia or meningitis was found more frequently in the non-19A group (45% vs. 11%, $p = 0.01$), and pneumonia with or without empyema occurred significantly more frequently in the 19A group (89% vs. 52%, $p = 0.006$). Patients in the 19A group had longer duration of fever (12 vs. 3 days, $p = 0.01$), and required more intensive care (78% vs. 41%, $p = 0.01$) and more video-assisted thoracoscopic surgery (74% vs. 28%, $p = 0.001$).

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Conclusion: In comparison with the other serotypes, serotype 19A IPD has significantly more empyema which required more video-assisted thoracoscopic surgery and more intensive care. Copyright © 2012, Taiwan Society of Microbiology. Published by Elsevier Taiwan LLC. All rights reserved.

Introduction

Invasive pneumococcal disease (IPD) is a very important disease in children and may cause significant morbidity and even fatality. Since seven-valent pneumococcal conjugate vaccine (PCV7) was launched, the incidence of IPD dramatically decreased in countries with nationwide immunization programs.^{1,2} However, the incidence of certain serotypes which were not covered by PCV7 increased significantly later on. The most common is the serotype 19A *Streptococcus pneumoniae*, which was observed to increase in incidence in United States.^{3,4}

In Taiwan, PCV7 was launched in October 2005, and it was self-paid vaccine, not covered by the national immunization program. The coverage rate of PCV7 among Taiwanese children aged ≤ 5 years was 0.7% in 2005, 8.6% in 2006, 15.9% in 2007, and 25.2% in 2008.⁵ Although the coverage rate of PCV7 was not high in Taiwan, we also observed the rising incidence of serotype 19A IPD in Taiwan.⁶ In addition, we found that the proportion of necrotizing pneumonia and empyema was high in cases with serotype 19A IPD. To delineate whether serotype 19A IPD would cause significantly more necrotizing pneumonia and empyema, we thus compared the clinical characteristics between serotype 19A and non-19A IPD.

Methods

Patient collection

IPD was defined when *S. pneumoniae* were recovered from a normally sterile site such as blood, pleural effusion, cerebrospinal fluid, or ascites by culture or polymerase chain reaction (PCR).⁷ Between January 2007 and December 2011, data on pediatric patients under 18 years with IPD in National Taiwan University Hospital were collected.

Clinical data collection

Patients were assigned to the 19A group or the non-19A group based on the serotype. Data pertaining to medical records, demographic details, clinical course, laboratory results, diagnosis, and complication of these patients were collected and analyzed. Respiratory failure was defined as the need for positive pressure ventilation. Pneumonia among patients of IPD was further looked up to find the presence of empyema, or necrotizing pneumonia. Empyema was defined as the presence of pus in pleural space diagnosed by pleurocentesis or video-assisted thoracoscopic surgery (VATS),⁸ and necrotizing pneumonia was defined as multiple small radiolucency or pneumatocele on

a chest radiograph or as cavities of non-enhancement on a contrast-enhanced CT image.⁹

Microbiological study

Antibiotic sensitivity was reported by disk-diffusion method and minimal inhibitory concentration tested using E-test. The interpretation was categorized according to the 2011 Clinical and Laboratory Standards Institute guidelines for breakpoints.¹⁰

Pneumococcal isolates were identified by the recognition of typical colony morphology on trypticase soy agar supplemented with 5% sheep blood (BBL Microbiology Systems, Cockeysville, MD, USA), Gram stain characteristics, susceptibility to ethylhydrocupreine hydrochloride (Optochin; Difco Laboratories, Detroit, MI, USA), and bile solubility. The isolate's serotype was determined with latex agglutination (Pneumotest-Latex, Statens Serum Institut, Copenhagen, Denmark).

Using blood and/or pleural effusion, PCR was performed optionally according to the primary care physician's clinical suspicion. Total nucleic acid was extracted from pleural effusion or blood specimens. Real-time PCR targeting the *wzj* gene was first performed to confirm the presence of *S. pneumoniae* DNA as previously reported.¹¹ Positive samples were included in the serotyping analysis by target gene PCR subsequently. Serotyping of serogroup 6 and serogroup 15 could only be done via latex agglutination but not PCR in our laboratory. Thus, some samples with positive PCR but negative culture only had serogroup recognized.

Statistics

Chi-square test with Yate's correction was used to compare the categorical data between the 19A and non-19A groups. Student's *t*-test was used to compare age and Mann-Whitney test was used for comparison of duration and laboratory data such as peak C-reactive protein level between the 19A and non-19A groups. A *p* value < 0.05 was considered statistically significant. All analyses were performed with SPSS version 18.0 (SPSS Inc., Chicago, IL, USA).

Results

Cases

Overall, 27 patients were included in the 19A group and 29 patients in the non-19A group. The non-19A group comprised serotype 3 (4 patients), serogroup 6 (1 patient), serotype 6A (2 patients), serotype 6B (2 patients), serotype 14 (4 patients), serogroup 15 (2 patients), serotype 15B

(3 patients), serotype 18C (1 patient), serotype 19F (9 patients), and serotype 23F (1 patient). No blood sample yielded positive PCR result. Eleven pleural effusion samples had positive PCR results but negative culture results. The yearly distribution of 19A and non-19A groups is shown in Fig. 1. The case number of 19A IPD tends to increase year by year ($p = 0.09$), especially in the year 2011.

Demography

Table 1 shows the demographic characteristics of the two groups. The mean age was about 4 years in both groups and the PCV7 vaccinated rate was 52% in 19A group and 43% in non-19A group. Compared with the non-19A group, *S. pneumoniae* serotype 19A tended to cause IPD in patients without major underlying diseases (Table 1, $p = 0.015$). Other demographic features were similar between the two groups.

Diagnosis

Bacteremia without pneumonia or meningitis was found more frequently in the non-19A group ($p = 0.01$). Most cases of bacteremia without pneumonia or meningitis had otitis and/or mastoiditis or sinusitis. Non-19A tended to have more occult bacteremia than the 19A group ($p = 0.07$). The 19A group accounted for significantly more pneumonia ($p = 0.006$) and empyema ($p < 0.001$) (Table 2).

Clinical course

The 19A group had longer duration of fever (12 vs. 3 days, $p = 0.01$) and higher peak C-reactive protein level (27.36 vs. 8.19 mg/dL, $p < 0.001$) than the non-19A group (Table 3). The ratio of leukocytosis, leucopenia, and thrombocytopenia did not differ significantly between the two groups. Although the incidence of respiratory failure, shock, and hemolytic uremic syndrome was not significantly different between two groups, patients of the 19A group were more often admitted to the intensive care unit. VATS was performed more frequently in patients of the 19A group ($p = 0.001$).

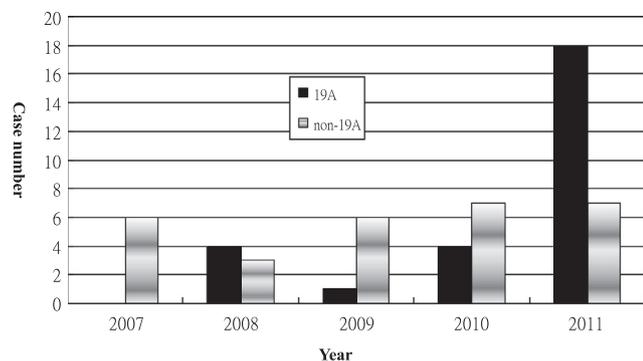


Figure 1. Yearly distribution of invasive pneumococcal disease caused by 19A serotype and non-19A serotype in 2007–2011.

Table 1 Comparison of demographic characteristics between 19A and non-19A invasive pneumococcal disease

	19A (N = 27)	Non-19A (N = 29)	p
Male/female	16:11	14:15	0.58
Age (mean \pm SD)	3.95 \pm 1.39	4.28 \pm 2.67	0.57
Kindergarten or daycare or school attendance	60% (15/25)	54% (15/28)	0.74
Major underlying disease	11% (3/27) ^a	41% (12/29) ^b	0.015
PCV7 vaccinated	52% (12/25)	43% (12/28)	0.70

PCV7 = pneumococcal seven-valent conjugate vaccine.

^a One patient had complex congenital heart disease, one had rhabdomyosarcoma, and another patient had chromosome anomaly (47, XXX).

^b There were four biliary atresia, three complex congenital heart disease, two severe aplastic anemia, one acute lymphoblastic leukemia, one methyl malonic academia, and one airway anomaly.

Outcome

Table 4 shows the final outcome and complication between two groups. There was one fatal patient in each group, and the mortality rate of the two groups was similar. Complications occurred in a similar ratio in both groups (15% in 19A group and 11% in non-19A group, $p = 0.92$) and only occurred in cases with necrotizing pneumonia. The complications included pneumatocele (6 patients), bronchopulmonary fistula (3 patients), and pneumothorax (3 patients). No patient received urokinase therapy.

Antimicrobial sensitivity

Disk method was used to define the sensitivity to erythromycin, moxifloxacin, levofloxacin, clindamycin, tetracycline, chloramphenicol, tigecycline, and vancomycin. There was no statistically significant difference between the two groups for the drugs discussed above. E-test was used to obtain the minimum inhibition concentration of penicillin, cefotaxime, vancomycin, and levofloxacin. The 19A group seemed to be less sensitive to cefotaxime than the non-19A group [6% (1/18) for 19A group, 32% (6/19) for non-19A group, $p = 0.09$]. Sensitivity to penicillin [53% (10/19) for 19A group, 63% (12/19) for non-19A group], levofloxacin [88% (7/8) for 19A group, 100% (2/2) for non-19A group], and vancomycin [100% (12/12) for 19A group, 100% (8/8) for non-19A group] were not significantly different between the two groups.

Discussion

We found that the case number of serotype 19A IPD increased in Taiwan after 2008 (Fig. 1). Empyema and necrotizing pneumonia occurred more frequently in serotype 19A IPD than in the non-19A group. Therefore, cases of 19A IPD had significantly longer hospitalization, and required significantly more intensive care and VATS.

After the launch of PCV7, the incidence of vaccine-type IPD markedly decreased.^{1,2} Later on, serotype replacement

Table 2 Clinical diagnosis between 19A and non-19A invasive pneumococcal diseases

Clinical diagnosis	19A (N = 27)	Non-19A (N = 29)	p
Bacteremia without pneumonia or meningitis	11% (3/27) ^a	45% (13/29) ^b	0.01
Occult bacteremia	4% (1/27)	24% (7/29)	0.07
Bacteremia with otitis, mastoiditis, or sinusitis	7% (2/27)	21% (6/29)	0.30
Pneumonia	89% (24/27)	52% (15/29)	0.006
Necrotizing pneumonia	33% (9/27)	14% (4/29)	0.16
Empyema	81% (22/27)	31% (9/29)	<0.001
Meningitis	0	3% (1/29)	0.96

^a One patient had concurrent acute otitis media and acute otitis externa, another patient had chronic sinusitis, and one had occult bacteremia.

^b Three patients had concurrent acute otitis media, and one patient had acute otitis media and acute mastoiditis. One patient had acute sinusitis, and another patient had chronic sinusitis and mastoiditis. The other seven had occult bacteremia.

Table 3 Comparison of clinical characteristics and data between 19A and non-19A invasive pneumococcal disease

Clinical characteristics/data	19A (N = 27)	Non-19A (N = 29)	p
Fever	100% (27/27)	100% (29/29)	NS
Duration, median (range)	12 d (3–39)	3 d (1–53)	0.01
Peak C-reactive protein (mg/dL)	27.36 (1.25–60.5)	8.19 (0.05–37.9)	<0.001
Respiratory failure	26% (7/27)	21% (6/29)	0.88
Shock	15% (4/27)	14% (4/29)	0.88
Hemolytic uremic syndrome	7% (2/27)	10% (3/29)	0.79
Hospitalization	96% (26/27)	97% (28/29)	0.93
Duration, median (range)	16.5 (7–71)	12 (1–156)	0.08
ICU care	78% (21/27)	41% (12/29)	0.01
Duration	5.5 (2–62)	4 (1–142)	0.42
VATS	74% (20/27)	28% (8/29)	0.001

ICU = intensive care unit; VATS = video-assisted thoracoscopic surgery; NS = not significant.

was found—that is, IPD caused by non-vaccine serotype 5 *pneumoniae* increased. The most commonly reported serotype is 19A.^{3,4} Taiwan as well as other countries are faced with the same serotype.^{5,6} Besides PCV7 selective pressure, an earlier study proposed that antibiotic use contributed to the emergence of serotype 19A in Taiwan.⁶

PCV13 broadens the serotype coverage including 19A, so we recommend PCV13 to be implemented in Taiwan's national immunization program in the future. Continuous monitoring of IPD epidemiology is still necessary since further serotype replacement (not covered by PCV13) may occur. The non-19A group in this study includes serotype 3, 6A, 6B, 14, 15B, 18C, 19F, 23F, and serogroup 6, 15. Most of these

serotypes could be prevented by PCV13 (except serogroup 15). PCV13 was released in April 2011 in Taiwan, and we hope that increased PCV13 coverage rate in the future will decrease the incidence of pediatric IPD in Taiwan.

Different serotypes of *S pneumoniae* may have different clinical severity. Serotypes 1 and 3 had been reported to be associated with the development of empyema and necrotizing pneumonia.^{12,13} In Taiwan, necrotizing pneumonia and empyema were associated with serotype 14 before PCV7 was introduced.⁹ After the introduction of PCV7, in spite of the decreased incidence of IPD, an increase in the incidence of empyema was observed.^{12,14} Serotypes 1, 3, and 19A played important roles in this suppurative complication in children.¹⁴ In this study, we found that serotype 19A also caused longer fever duration, higher C-reactive protein, as well as significantly more empyema, which required more intensive care and VATS than the other serotypes of pneumococci. Hsieh et al^{6,15,16} also reported that serotype 19A was strongly associated with high invasive potential and severe necrotizing pneumonia and bronchopleural fistula. In contrast, non-19A groups tends to have bacteremia without pneumonia/meningitis, and most cases had otitis-origin infection or occult bacteremia in our study.

In conclusion, serotype 19A IPD accounted for more severe pneumonia such as empyema, which requires more

Table 4 Clinical outcome between 19A and non-19A groups

	19A	Non-19A	p
Mortality	4% (1/27)	3% (1/29)	0.50
Complete recovery	81% (22/27)	86% (25/29)	0.91
Complication	15% (4/26)	11% (3/28)	0.92
Pneumatocele	15% (4/27)	7% (2/28)	0.63
Bronchopulmonary fistula	4% (1/27)	7% (2/28)	0.97
Pneumothorax	4% (1/27)	7% (2/29)	0.95

intensive care and thoracic surgery. The high prevalence of serotype 19A among IPD in Taiwan indicates the serotype replacement after PCV7 and the importance of 19A inclusion in PCV13 for serotype 19A IPD prevention.

Conflicts of interest

All contributing authors declare no conflicts of interest.

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