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SHORT REPORT

Invasive pneumococcal disease: From a tertiary care hospital in the post-vaccine era

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ABSTRACT

A breakthrough infection occurring with 13-valent pneumococcal conjugate vaccine (PCV13) in Turkey are previously described. A breakthrough infection is defined as IPD in a child who had received ≥ 1 PCV-7 or PCV-13 and for which the pneumococcal isolate was a vaccine serotype. During one year period, among 6 patients with invasive pneumococcal infection, 2 patients were considered to have a vaccine failure with serotype 19F. Antibiotic resistance results were remarkable; macrolide resistance were observed in all strains except one, and high and intermediate penicillin resistance were determined in 2 strains.

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Streptococcus pneumoniae (S. pneumoniae) has the potential to cause local respiratory tract illnesses, such as acute otitis media, acute sinusitis, and non-bacteremic pneumonia in children, or to enter the bloodstream and result in a series of diseases, such as bacteremia, sepsis, and meningitis. Although patients with invasive pneumococcal disease (IPD) present less commonly with meningitis, case fatality rates are high and neurological morbidity is frequently found in survivors.

Pneumococcal antibiotic resistance is a worldwide challenge owing to the ongoing burden of disease, despite the increment in the rate of highly effective vaccinations. Serotype replacement after the administration of the conjugate vaccines and an escalation in antibiotic resistance remain important issues in terms of their impact on clinical outcomes in pneumococcal disease.

Thus, in the context of these data findings, the objective of our study was to analyze patients with IPD at our institution over a one-year period.

Our hospital is a tertiary referral hospital and our department has led an analysis of hospital-based pneumococcal surveillance across Turkey since 2008. The medical records of cases aged ≤ 18 y and diagnosed with IPD by pediatric infectious disease specialists between January 2015 and January 2016 at Hacettepe University İhsan Doğramacı Children's Hospital were retrospectively reviewed. The study was approved by the Ethical Committee of Hacettepe University. IPD cases were eligible for evaluation if *S. pneumoniae* had been isolated from a normally sterile body site. The data for age, gender, underlying diagnosis, type of pneumococcal clinical syndrome, serotype, antibiotic susceptibility of the bacteria to penicillin, immunization status of the patients with regard to pneumococcus, length of treatment, and length of hospital stay were obtained. The isolates were subjected to disc susceptibility tests for penicillin, macrolides, and fluoroquinolones, according to the guidelines of the Clinical and Laboratory Standards Institute.[1] Minimum inhibitory concentration (MIC) was established using an Epsilometer test (E-test, Biomerieux, S.A.S.).

All of the patients diagnosed with IPD were identified as male, with a median age of 28 months (a range of 2–61 months) during the study period, from January 2015 to January 2016. Underlying disease was found in all of the patients, with the exception of 2 (cases 1 and 2). One of the patients with oncological malignancy (case 3) was undergoing chemotherapy. The other diagnoses were inherited metabolic disorder (case 4), congenital hydrocephalus with ventriculoperitoneal shunt (case 5), and cerebral palsy secondary to intracranial bleeding (case 6). Three patients presented with meningitis (cases 1, 2 and 5), 2 patients with bacteremia (cases 3 and 4), and one with pneumonia (case 6).

It was found on investigation into the patients' immunization status that the one with oncological malignancy had not received a pneumococcal vaccination. Two patients (cases 5 and 6) had been vaccinated with 3 doses of 13-valent pneumococcal conjugate vaccine (PCV13) and one (case 2) with 3 doses of the 7-valent pneumococcal conjugate vaccine (PCV7). All three patients had received a booster dose.

Two patients, aged 2 months (case 1) and 8 months' (case 4) had received a single dose of PCV13 and 3 doses of PCV13, respectively. All of these vaccinations had been administered appropriately in accordance with their ages.

The median length of antibiotic treatment was 16 d (min-max = 6–24 months) and the median length of hospitalization was 28.5 d (min-max = 6–48 days). At the end of treatment, for 2 cases (case 5 and 6) the outcome was fatal where for 2

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meningitis cases (case 1 and 2) neurologic sequelae occurred. Serotype 19F was observed following an investigation into cases 5 and 6 and attributed to vaccine failure (Table 1).

High and intermediate resistance to penicillin was observed in 2 cases. Antibiotic susceptibility and the individual MIC values are demonstrated in Table 1. Macrolide resistance was observed in all strains, except one. Fluoroquinolone resistance was not found in any of the strains.

PCV7, included in the Childhood National Immunization Program in Turkey in November 2008, was replaced with PCV13 in February 2010. Following the introduction of PCV13 to the childhood immunization program, the vaccination rate for the 3 doses reached 96%.[2] Since 2008, 22 hospitals, located in 7 regions in Turkey, have been screened with the use of an active pneumococcal surveillance system. Pneumococcus strains of the patients analyzed in the present study were typed in this surveillance system. Although only a small number of patients were included in our study, since our hospital is a referral hospital, the data are invaluable in highlighting severe IPD cases in the region. The most prevalent clinical syndrome was meningitis, followed by bacteremia and sepsis. Non-vaccine serotypes (15B, 18F, and 1) were found in 4 of the cases, drawing attention to the emergence of non-vaccine serotypes as the cause of IPD. Determination of the invasive disease potential of individual serotypes has been studied since 2000 in relation to the availability and provision of PCV7. In one study, significant invasive indices for IPD were identified with vaccine serotypes 4, 14, and 18C (present in PCV7 and PCV13) and 1, 5, 7F, and 19A (present in PCV13).[3] A decrease in the incidence of IPD has been reported in all the countries in which PCVs have been introduced. A reduction in IPD has been attributed to the reduction in vaccine-type IPD. However, it has been reported elsewhere that global efficacy against pneumococcal infections has partially been diminished by the increase in non-vaccine-type IPD.[4,5] It was reported in a recent study that the number of serotypes with high disease potential decreased following the administration of PCV13 in infants aged $\leq$ 2 y. Only six serotypes, 24F, 19A, 12F, 15B/C, 10A, and 15A, represented 60.7% of IPD cases.[3] In the Turkish pneumococcal disease surveillance system, the proportion of non-vaccine serotypes was stated to be 27% in the 2008–2011 period and 38% in 2011–2014 period. There was a significant reduction (20%) in the number of isolates in the latter period, possibly owing to the impact of the national pediatric vaccination program which included PCVs,[6,7]

Two of the patients in the current study who had completed the age-appropriate PCV13 vaccine series acquired serotype 19F, indicative of a vaccine breakthrough. Underlying neurological diseases were present in both of these patients who died during treatment. A breakthrough infection is defined as IPD in a child who had received $\geq$ 1 PCV7 or PCV13, of which the pneumococcal isolate is a vaccine serotype. Park *et al.* reported on vaccine breakthrough of 21% in their series, predominantly caused by serotypes 6B and 19F.[8] Vaccine breakthrough was reported to be 3% of meningitis cases in France.[9] Ceyhan *et al.* cited a vaccine breakthrough figure of 25% in Turkey from 2008–2014.[7] These study findings support those found in 2 of our cases.

S. pneumoniae has developed resistance to a myriad of antibiotics, including β-lactams, macrolides, and fluoroquinolones. Antimicrobial resistance in pneumococcus causes changes to the clinical presentation of disease, making it more difficult to diagnose and to treat. The resistance patterns associated with pneumococcal infections vary considerably between geographical areas and develop over time. In surveillance throughout Europe, Navarro *et al.* reported the highest rates of non-susceptibility to penicillin in Romania (42%), Cyprus (36%), and France (28%) in 2010. The highest rates of non-susceptibility to penicillin were reported to be 47%, 28%, and 26%, in Romania, Spain, and Croatia, respectively, in 2014, by the European Surveillance System.[10]

Macrolide resistance is increasing at an alarming rate. It was demonstrated in 56% of isolates from 19,000 strains according to the SENTRY Antimicrobial Surveillance Program.[11] Promising results pertaining to fluoroquinolone resistance (of only 1% in 2011) are highlighted in the same report. This is probably because fluoroquinolones are not recommended in children who are a major reservoir for pneumococci. Fluoroquinolone resistance was not demonstrated in any of the pneumococci in the present study, whereas macrolide susceptibility was found in a single strain. Intermediate and high resistance to penicillin was observed in 2 patients. Rational antibiotic usage in clinical practice is urgently required in Turkey since the percentage for the prevalence of pneumococcal antibiotic resistance is higher than that reported in Europe.

In conclusion, greater efforts are required to combat *S. pneumoniae*. Proper diagnosis of IPD cases, definition of microbiological characteristics of pneumococci, and follow up of disease prognosis are crucial steps for improving the knowledge of the

Table 1. The characteristics of patients with invasive pneumococcal disease.

	Age (months) / gender	Underlying diagnosis	Clinical syndrome	Serotype of pneumococcus	Previous PCV type/dose	Length of treatment (days)	Length of hospitalization (days)	Outcome / Any sequela	Antibiotic susceptibility profiles		
									Penicillins	Macrolides	Fluoro.
Case 1	2, Male	No	Meningitis	15B	PCV13/ 1	23	36	Alive/yes	HR	R	S
Case 2	61, Male	No	Meningitis	1	PCV7/ 3 + 1	14	21	Alive/yes	S	S	S
Case 3	51, Male	Oncological malignancy	Bacteremia	1	Not vaccinated	18	48	Alive/no	IR	R	S
Case 4	8, Male	IMD	Bacteremia	18F	PCV13/ 3	24	36	Alive/no	S	R	S
Case 5	13, Male	Hydrocephalus with VP shunt	Meningitis	19F*	PCV13/ 3 + 1	6	6	Exitus	IR	R	S
Case 6	43, Male	Cerebral palsy	Pneumonia	19F*	PCV13/ 3 + 1	12	12	Exitus	HR	R	S

IMD: Inherited metabolic disorder, VP: Ventriculoperitoneal shunt, HR: High resistance, IR: Intermediate resistance, Fluoro.: Fluoroquinolones, S: Susceptible, R: Resistant, *Vaccine failure.

emerging serotypes, determination of their invasive diease potentials, and revealing vaccine failure. Our study findings were invaluable in highlighting aforementioned features of IPD in our region. Still larger, more extensive surveillance studies are required to corroborate our results for planning effective vaccination strategies.

Abbreviations

S. pneumonia	Streptococcus pneumonia
IPD	Invasive pneumococcal disease
PCV-13	13-valent pneumococcal conjugate vaccine
PCV-7	7-valent pneumococcal conjugate vaccine
MIC	Minimum inhibitory concentration

Disclosure of potential conflicts of interest

None of the authors have anything to declare.

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