FACTORS ASSOCIATED WITH ACQUIRING PENICILLIN NONSUSCEPTIBLE INVASIVE PNEUMOCOCCAL DISEASE IN LOS ANGELES COUNTY

INTRODUCTION

In September 1995, the Los Angeles County (LAC) Department of Health Services initiated a laboratory and hospital infection control-based surveillance project for ten diseases and conditions including invasive pneumococcal disease (IPD), which is not a California state-reportable disease. Data showed that the annual incidence of reported IPD went from 8.4 cases in 1996 to 8.9 cases per 100,000 in 1999 and back down to 8.2 in 2000; the proportion of penicillin-resistant isolates increased from 19% to 29% and decreased to 24%, respectively in the same years. These findings are consistent with results from a recent 1997 study from seven metropolitan areas in the U.S. which showed that the proportion of penicillin-resistant isolates varied from 15% to 39%.[1]

This study examined risk factors associated with acquiring drug-resistant IPD for hospitalized LAC residents. The goal was to identify populations at risk for acquiring drug-resistant *S. pneumoniae* so strategies can be developed for prudent usage of antibiotics and efficient allocation of vaccine.

METHODS

The 1998 IPD surveillance data with antimicrobial susceptibility results (N=659) were merged with 1998 patient discharge data made available from the State of California Office of Statewide Health Planning and Development (OSHPD). Pneumococcal disease and underlying diseases were examined using codes as defined by the International Classification of Diseases, 9th Revision, Clinical Modification, U.S. Department of Health and Human Services, Washington D.C. (ICD-9-CM). The 1998 IPD surveillance data, which contained patient identifying information, were matched with OSHPD data by the facility name where the patient was hospitalized, age in years for date of birth, day of week, month and year of admission for admission date, and a truncated three-digit ZIP Code of residence.

A case-control study was performed. A case was defined as a LAC resident with a positive culture of penicillin-nonsusceptible (intermediate or high-level resistance) *S. pneumoniae* (PNSP) collected in 1998 from a normally sterile site and who was hospitalized at a LAC acute care hospital. A control was a hospitalized individual with a positive culture of penicillin-susceptible *S. pneumoniae* (PSSP) from a normally sterile site and collected in 1998.

Data were analyzed using Epi-Info 6.04 and SAS Version 6.12. A p-value of <0.05 was considered to be statistically significant. A map of cases and controls by place of residence was generated using MapInfo Version 3.0 software.

RESULTS

Forty-three percent (283) of the IPD surveillance cases were matched to the OSHPD data. When matched and unmatched IPD cases (N=376) were compared, there was no significant difference in gender (OR=0.93; CI: 0.67 to 1.28), culture site (OR=1.25; CI: 0.56 to 2.78), and rate of penicillin nonsusceptibility (OR=1.14; CI: 0.78 to 1.66) between the two groups. IPD cases less than 18 years were significantly less likely to be included in the study than adults over 18 years (OR=0.21; CI: 0.14 to 0.32).

In the study population (Table 1), 144 males and 139 females were aged 3 months to 99 years (mean ± SD, 55 ± 28 years). Whites constituted the majority of the patients (53%) followed by Blacks (17%) and Hispanics (16%). Forty-seven percent (134) were 65 years and over, 21% (59) were 45 to 64 years, 17% (48) were 15 to 44 years and 14% (39) were less then five years. *Streptococcus pneumoniae* was isolated from blood in 95% (269) of the patients, cerebral spinal fluid (CSF) in 4% (12), and other sterile sites in less than 1%, including one from joint/synovial fluid and one from chest fluid. The proportion of patients identified with isolates not susceptible to penicillin was 25% (72). Patients stayed in the hospital an average of nine days (s.d. ± 7). The majority of patients were admitted from home (92%) with an additional 14 patients referred from long-term care facilities. Seventy-four percent of the patients had one or more underlying medical conditions; the most frequent were pulmonary disease (38%), followed by cardiac disease (32%), malignancy (19%), and diabetes mellitus (15%). The most frequent expected source of payment for hospitalization reported were Medicare (42%), health maintenance organizations or preferred provider organizations (30%), and Medi-Cal or County Indigent Program (22%).

Seventy-two eligible cases with PNSP and 211 controls with PSSP were identified and compared. The cases did not differ significantly with respect to race/ethnicity, gender, and the other factors listed in (Table 2). Compared with controls, cases appeared to cluster geographically around the southwest portion of LAC (Map 1). Service Planning Area 5 (SPA 5) had the highest proportion of penicillin resistance for *S. pneumoniae* (45%), followed by SPA 4 (35%) and SPA 5 (27%).

Although the association between outcome and penicillin nonsusceptibility was not significant, more deaths occurred in the controls indicating that patients with PNSP were less likely to die then patients with PSSP (OR=0.85; CI: 0.38 to 1.86). Also, patients that were admitted with PNSP were less likely to have an underlying medical condition although the association was not significant (OR=0.89; CI:0.47 to 1.71). There was no difference in length of stay for cases and controls (Table 2).

Compared to PSSP patients, PNSP patients were significantly associated with being young and there was borderline significance with being very old. Patients who were 65 years and older and patients less than 18 years old were more likely than patients 18-64 years to be diagnosed with penicillin nonsusceptibility (OR=1.83, 95% CI: 0.94 to 3.58 and OR=2.57, 95% CI: 1.07 to 6.19) (Table 2). In addition, among those 60 years and over, PNSP cases were not significantly more

likely than controls to have been admitted from a long-term care facility versus from home (OR=1.07; 95% CI: 0.23 to 4.04).

DISCUSSION

ACDC identified four important findings regarding penicillin nonsusceptible IPD in LAC:
(1) nonsusceptibility occurred in 25% of the patients, (2) nonsusceptibility varied by SPA, (3) nonsusceptibility was associated with patients less than 18 and older than 65 years, and (4) nonsusceptibility was not associated with increased mortality.

Zangwill et al. published the most recent study assessing IPD and penicillin nonsusceptibility in LAC.[13] They examined three years of data (April 1992 to March 1995) from the Kaiser Permanente Southern California Region (health maintenance organization) that included LAC and seven other contiguous counties. In their population-based study, they found 14% penicillin nonsusceptibility. The health department's surveillance system for IPD, which include inpatients and outpatients, observed annual penicillin nonsusceptibility rates that fluctuated from 20%, 29%, and 24% in 1996, 1999, and 2000. Our study examined only hospitalized cases and determined that the proportion of hospitalized patients with PNSP (25%) was not substantially different from what was observed for all the cases reported in 1998 to the IPD surveillance system in 1998 (24%). The trend of increasing resistance toward penicillin in LAC appears to have almost doubled from what was first reported by Zangwill. In a study of 34 medical centers throughout the U.S. in 1998, the rate of resistance to penicillin was 29.5%, which is slightly higher than the rate we observed.[3]

Numerous studies have identified children less than five years and adults over 65 years at a higher risk for penicillin nonsusceptibility.[5,6,9] Risk factors for penicillin resistance have often been associated with extremes of age. Studies have recognized exposure to a day care center,[7] exposure to a long-term care facility,[6] and underlying medical condition[9] as risk factors for PNSP. In this study, PNSP cases were not associated with exposure to a long-term care facility or the presence of an underlying condition although the numbers were small for the former. No data on day care exposure were obtained for this study. Other factors elucidating the mechanisms for the increased incidence of penicillin resistance in the very young and old in LAC will have to be studied.

Some limitations of the OSHPD data may have affected the conclusions drawn in this study. First of all, matching cases in the IPD surveillance and OSHPD data were difficult because OSHPD data were incomplete for confidentiality purposes (no date of birth, truncated ZIP code, etc.). Also, there was a potential for miscoding in the OSHPD data. Problems with misclassifying diagnosis codes may have occurred with underlying medical condition. It is unknown whether there was coding variation between hospitals. Other studies that recovered their data directly from reviewing medical records found an association between penicillin resistance and underlying condition. Our study relied heavily on the OSHPD data, which may have contributed to not finding a difference with regard to underlying medical condition. Also, persons under 18 years old were less likely to be included in the study. This could be a consequence of using OSHPD data because children are

hospitalized less frequently and have fewer underlying medical conditions that could complicate their illness. In addition, known risk factors such as previous antibiotic usage[2,4,8-10] and prior hospitalization[12] were not available in the OSHPD data. Further studies are needed to determine whether these same risk factors are associated with penicillin nonsusceptibility in LAC.

The overall mortality in this study was 17%, which is consistent with findings from other studies.[5,6,11] Mortality appeared to be less in PNSP patients than with PSSP patients (15% vs. 18%) but the association was not significant. The role of drug resistance for IPD on mortality remains unclear. Most studies of IPD have not demonstrated an association between antibiotic resistance and increased mortality. Turett et al.[11] were the first to report penicillin resistance as an independent predictor of mortality among hospitalized patients with pneumococcal bacteremia. It should be noted that half of the cases in Turett's study had human immunodeficiency virus (HIV) infection whereas in this study 2% were infected with HIV. Further study is needed. Although not supported by our study, if penicillin resistance is a predicator of mortality, it lends support for targeting groups who are at high risk for acquiring drug-resistant IPD for vaccination because of increased probability of poor clinical outcome.

With the widespread overuse of antibiotics, the problem of microbial drug resistance will continue to increase as a major public health threat. It is through educational programs targeting the community and medical establishment about proper antibiotic usage that we must attempt to reduce the growing numbers of drug-resistant pathogens. In addition, vaccination campaigns utilizing the recently Food and Drug Administration-approved pneumococcal conjugate vaccine for very young children and the pneumococcal polysaccharide vaccine for the elderly and high-risk individuals must be utilized to decrease the incidence of those at high risk for not only penicillin resistance but also IPD.

TABLE 1: Demographic Statistics of Hospitalized Cases of IPD, LAC, 1998 (N = 283)

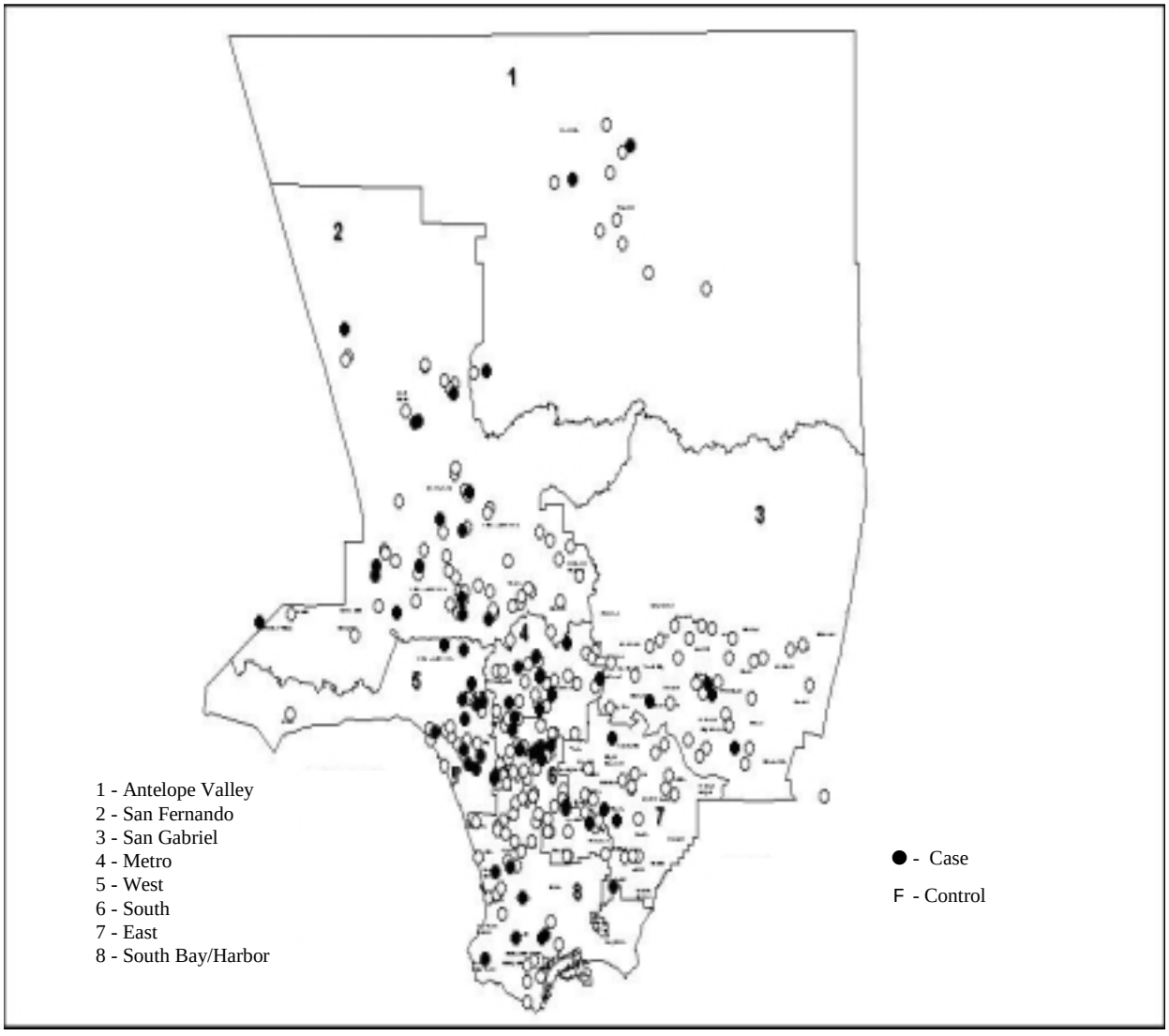
Characteristics			**%**
Race	African American		17
	Asian		3
	Hispanic		16
	White		53
	Other		10
	Unknown		1
Gender	Male		51
	Female		49
Age	< 5		14
	5 –14		1
	15 – 44		17
	45 – 64		21
	65 +		47
Mean Age (in years)			55 (s.d. 28)
Source of admission	Home		92
	Long-term Care Facility		5
	Acute Inpatient Hospital Care		3
Mean length of stay (in days)			9 (s.d. 7)
Expected source of payment for hospitalization			
Medicare			42
Medi-cal/County Indigent Program			22
HMO/PPO			30
Private insurance			3
Self-pay			2
Military			<1
Underlying medical conditions		Yes	74
		No	26
Outcome	Died		17
	Survived		83
Penicillin nonsusceptibility		Yes	25
		No	75

TABLE 2: Characteristics Associated with Having IPD Nonsusceptible to Penicillin (N = 283)

Characteristics		Nonsusceptible n	Nonsusceptible %	Susceptible n	Susceptible %	p-value*
Race	African American	14	20	33	16	.86
	Hispanic	10	14	35	17	
	White	38	54	110	53	
	Other	9	13	29	14	
Gender	Men	40	56	104	49	.36
	Women	32	44	107	51	
Age (in years)	< 18	15	21	27	13	.04
	18 – 64	19	26	88	42	
	65 +	38	53	96	46	
Source of admission (≥60 years, n=143)						.56**
	Long-term care facility	4	10	10	10	
	Home	35	90	94	90	
Length of stay (in days) Mean ± sd		9 ± 6		9 ± 7		.73***
Outcome	Died	11	15	37	18	.66
	Survived	61	85	174	82	
Underlying medical condition	Yes	52	72	157	74	.72
	No	20	28	54	26	

*Pearson's χ^2 used unless otherwise noted. **Fisher's Exact Test. ***Wilcoxon 2-Sample Test.

MAP 1. Map of place of residence for PNSP cases (black dots) and controls (white dots). The bold-faced numbers and boundaries represent service planning areas (SPAs) in Los Angeles County. Six percent (4) of the cases and 2% (4) of the controls could not be mapped.



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