Invasive Penicillin-Resistant Pneumococcal Infections: A Prevalence and Historical Cohort Study

More than 25 years ago, isolates of *Streptococcus pneumoniae* were uniformly susceptible to penicillin. However, since a penicillin-resistant pneumococcus was first identified in 1967 (1), the incidence of penicillin-resistant *S. pneumoniae* (PRSP) strains has been gradually increasing. In certain areas of the United States, PRSP strains have become widespread; Alaska has the highest reported prevalence, 26% (2); a recent study conducted in Atlanta, Georgia, found a 25% prevalence of PRSP (3). Outside the United States, an even higher (33%-58%) prevalence of PRSP has been reported (2).

Pneumococcal infections are a leading cause of morbidity and mortality in the United States. *S. pneumoniae* causes more than 500,000 cases of pneumonia, 55,000 cases of bacteremia, and 6,000 cases of meningitis annually, which result in 40,000 deaths (4). The death rate from pneumococcal bacteremia approaches 30%, despite the use of appropriate antimicrobial therapy (5). Reports of refractory illness due to resistant pneumococci demonstrate the clinical relevance of these strains (6,7). Identifying risk factors in the development of PRSP infections is important for both the prevention and treatment of these infections.

The prevalence of invasive infections due to PRSP was previously studied in Denver, Colorado (8,9). We undertook the study described here to determine the prevalence of invasive PRSP infections in the Colorado Front Range and to determine whether invasive PRSP infections have increased in metropolitan Denver since the earlier studies. In addition, we studied a cohort of patients who had invasive pneumococcal disease during 1994 in metropolitan Denver to ascertain risk factors for invasive PRSP infections.

Twenty-six hospital microbiology laboratories in the Colorado Front Range, which comprises the 10 largest counties in Colorado and 80% of the state's population (10), submitted to the Colorado Department of Public Health and Environment reports of all blood and cerebrospinal fluid (CSF) isolates of *S. pneumoniae* that were tested for penicillin susceptibility during 1994. (Penicillin susceptibility testing on invasive pneumococcal isolates was standard practice for the laboratories and did not depend on a clinician's request.) For the part of the study that assessed prevalence, penicillin resistance was defined as a minimum inhibitory concentration (MIC) of ≥ 0.12 µg/ml or an oxacillin zone of inhibition < 20 mm. Isolates that were tested by an MIC method were further classified as intermediately (0.12 µg/ml-1.0 µg/ml) or highly (≥ 2.0 µg/ml) penicillin resistant. For the part of the study in which the cohort was analyzed, only isolates that were confirmed as penicillin resistant (i.e., MIC ≥ 0.12 µg/ml) by either broth dilution or the E test (AB Biodisk, North America, Inc., Culver City, California) were included. Data for the cohort study were collected by chart review by the principal investigator, and telephone interviews of patients were conducted by trained interviewers in the Health Statistics Survey Research Unit of the Colorado Department of Public Health and Environment. For patients under 18 years of age, a parent or legal guardian was interviewed. When patients had died, a relative of the patient (if available) was interviewed.

Invasive pneumococcal infections were found in 363 patients in the Colorado Front Range; 49 (13%) of the infections were resistant to penicillin. In metropolitan Denver, 29 (14%) of the invasive pneumococcal infections were penicillin-resistant, of which 20 (69%) were intermediately penicillin-resistant (i.e., MIC 0.12-1.0 µg/ml), and 9 (31%) were highly penicillin-resistant (i.e., MIC ≥ 2.0 µg/ml). This prevalence rate of invasive PRSP infections is significantly higher than the previously reported rates in Denver of 1% (8) and 7% (9). Previous surveillance of invasive PRSP isolates showed that one region in the United States, which included Colorado, had a significantly higher rate of penicillin resistance among pneumococcal isolates than other U.S. regions (11).

Half of the PRSP strains in the cohort part of the study that were tested for cephalosporin susceptibility were resistant to an extended-spectrum cephalosporin. Our results are similar to the recent Atlanta study which found that 34% to 54% of PRSP infections were resistant to an extended-spectrum cephalosporin (3). These rates are much higher than other reported rates of cephalosporin resistance among PRSP isolates of 27% in Kentucky and 25% in Tennessee, (12). This has important implications for the management of invasive

PRSP infections, especially in meningitis, where MICs of ß-lactam antibiotics in the cerebrospinal fluid may be less than the MICs of ß-lactam antibiotics in the blood (13). The Centers for Disease Control and Prevention recommends that in areas where pneumococcal resistance to cephalosporins is high, empiric therapy with vancomycin plus an extended-spectrum cephalosporin should be considered in all cases of meningitis potentially caused by *S. pneumoniae*, until the results of culture and susceptibility testing are available (14).

A number of studies have addressed the clinical relevance of PRSP infections and have attempted to identify predictive factors for the development of these infections. In our analysis of the demographic and clinical characteristics of the study population (Table), we found that day-care attendance by a member of the patient's household in the 3 months before the patient's illness was associated with invasive PRSP infections. Indeed, 26% of patients with PRSP infections, compared with 7% of patients with penicillin-sensitive infections, had at least one member in their household, excluding the patient, who had been attending a day-care center before becoming ill.

Table. Demographic and clinical characteristics of patients with invasive penicillin-resistant *S. pneumoniae* (PRSP) and penicillin-sensitive *S. pneumoniae* (PSSP) infections

	PRSP; n = 29 (%)	PSSP; n = 180 (%)	Odds ratio (95% confidence interval)
Demographic characteristics			
Age, years			
< 5	11 (38)	39 (22)	1.9 (0.4-9.1)
5-64	8 (28)	93 (52)	Reference
> 64	10 (34)	48 (27)	1.9 (0.5-7.1)
Sex			
Male	12 (41)	104 (58)	Reference
Female	17 (59)	76 (42)	1.8 (0.6-5.4)
Race[a]			
White	16 (55)	100 (56)	Reference
Nonwhite	11 (38)	68 (38)	1.4 (0.5-3.9)
Clinical characteristics			
Site of infection			
Blood	26 (90)	171 (95)	Reference
CSF	3 (10)	9 (5)	0.8 (0.1-5.1)
Underlying medical condition	14 (48)	108 (60)	1.0 (0.3-3.2)
Antibiotic use[b]	14 (52)	56 (39)	2.5 (0.9-7.1)
No history of penicillin allergy[c]	26 (90)	163 (91)	0.7 (0.1-3.4)
Previous hospitalization[d]	5 (19)	33 (23)	0.3 (0.1-1.5)
Day-care attendance			
Patients < 11 years[e]	5 (50)	19 (50)	1.1 (0.4-2.7)
Household member(s)[f]	7 (26)	10 (7)	8.1 (2.2-30.7)
Residence in a long-term care facility (patients > 64 years)[g]	2 (20)	13 (27)	0.7 (0.1-3.6)
Hospital-acquired infection	1 (3)	8 (4)	0.4 (0.04-4.9)
Outcome			
Survived	25 (86)	156 (87)	Reference
Died	4 (14)	24 (13)	1.6 (0.4-6.3)

[a] Missing information on 2 PRSP and 12 PSSP patients.

[b] Includes patients who had taken an antibiotic in the 3 months before illness; missing information on 2 PRSP and 36 PSSP patients.

[c] Missing information on 1 PSSP patient.

[d] Patients who were hospitalized in the 3 months before illness; missing information on 2 PRSP and 34 PSSP patients.

[e] Children < 11 years of age who attended day care in the 3 months before illness; children < 11 years of age, N = 56 (PRSP = 12, PSSP = 44); missing information on 2 PRSP and 6 PSSP patients.

[f] Patients with at least 1 child < 11 years of age (excluding the patient) in the household who attended day care in the 3 months before illness; missing information on 2 PRSP and 39 PSSP patients.

[g] Adults > 64 years of age who resided in a LTC facility in the 3 months before illness; adults > 64 years of age, N = 58 (PRSP = 10, PSSP = 48).

This study is unique in that, to our knowledge, day-care attendance among household members of patients has not been studied. Even though most studies have not specifically considered family members as a potential mode of PRSP transmission, rates of nasopharyngeal carriage of PRSP are significantly higher in family contacts of children colonized with PRSP who were attending day-care centers (7, 15).

Our finding that patients with PRSP infections were more likely to have had a child in their household who had attended day-care during the months before their illness suggests that day-care settings may serve as foci for spreading resistant pneumococcal strains. Antibiotics are extensively used to treat upper respiratory infections that children attending day-care centers often have; the practice of administering a prolonged course of prophylactic antibiotics to children with recurrent otitis media who

attend day-care centers (16) may promote the selection of resistant bacteria in these settings (6, 15). These children may subsequently transmit resistant *S. pneumoniae* to susceptible persons in their households. Thus, patterns of antibiotic treatment of children who attend day-care centers may explain why day-care attendance might facilitate PRSP transmission. The likelihood that day-care settings may serve as reservoirs for antibiotic-resistant pneumococci indicates that the efficacy of prophylactic antibiotics for otitis media should be reassessed, especially when PRSP is present in a community.

Furthermore, carriage of or infection with PRSP has been associated with recent use of antibiotics (17). Our study showed that patients with PRSP infections were more likely to have taken an antibiotic in the 3 months before their illness than patients with penicillin-sensitive pneumococcal infections. This finding supports the theory that antibiotic resistance has developed because of the widespread availability and use of antibiotics. Since the beginning of the antibiotic era 50 years ago, it has been well recognized that antibiotics have been and continue to be inappropriately used (18).

The emergence of drug-resistant *S. pneumoniae* emphasizes the importance of following the recommendation of the Immunization Practices Advisory Committee that all persons 2 years of age and older who are at high risk for pneumococcal disease receive the 23-valent pneumococcal capsular polysaccharide vaccine. Because of its lack of immunogenicity and efficacy, the pneumococcal vaccine has not been licensed for children under 2 years of age (14). The high prevalence of PRSP among young children (3, 17), and the potential for these children to transmit PRSP to susceptible persons, underscore the need for an effective pneumococcal vaccine for this age group.

Antimicrobial resistance contributes to increased morbidity, mortality, and health care costs (19). The solution lies in changing antibiotic prescribing patterns, changing patient attitudes about the necessity of antibiotics, increasing surveillance of drug-resistant organisms, improving techniques for antibiotic susceptibility testing, and investing in research and development of newer antimicrobial agents.

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