Penicillin-Nonsusceptible *Streptococcus pneumoniae* at San Francisco General Hospital

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Positive pneumococcal cultures of specimens from adult inpatients at San Francisco General Hospital (SFGH) during the period of 11 August 1994 through 31 December 1996 were identified retrospectively. Of the isolates recovered, 15.5% were not penicillin-susceptible (MIC, $\geq 1 \mu g/mL$). A case-control study was performed to evaluate risk factors for colonization or infection with penicillin-nonsusceptible *Streptococcus pneumoniae* (PNSP) and outcomes. Cases ($n = 65$) were adult inpatients with a positive culture for PNSP, and controls ($n = 411$) were adult inpatients with a positive culture for penicillin-susceptible pneumococci (PSSP) and no evidence of PNSP. Cases were less likely to have pneumococcal bacteremia (15.4% versus 39.4%; $P < .001$) and less likely to have pneumonia (50.8% versus 68.9%; $P = .006$). In a multiple logistic regression model, recent hospital admission and absence of bacteremia were independent predictors of penicillin-nonsusceptibility. Human immunodeficiency virus infection, mortality, and length of hospitalization were not significantly different among cases and controls. These data suggest that PNSP may be less virulent (cause less pulmonary infection) and/or less invasive (cause fewer bloodstream infections) than PSSP at SFGH.

*Streptococcus pneumoniae* clinical isolates with reduced susceptibility to penicillin first appeared in the late 1960s, and concerns about this organism have escalated in the 1980s and 1990s. These strains of penicillin-nonsusceptible *S. pneumoniae* (PNSP) have a penicillin MIC of $\geq 1 \mu g/mL$ and are often resistant to several other antibiotics, including tetracycline, erythromycin, extended-spectrum cephalosporins, and chloramphenicol [1]. Highly penicillin-resistant strains (MIC, $\geq 2 \mu g/mL$) are more likely to be resistant to multiple antibiotics than are those with intermediate susceptibility (MIC, 0.1 $\mu g/mL$–1 $\mu g/mL$) [2, 3].

In the United States, children younger than 4 years old, especially those in day-care and other group settings, are at highest risk for acquiring PNSP. Among hospitalized children, prior hospitalization, length of hospital stay, and frequent antibiotic use have been associated with infections caused by nonsusceptible strains [4]. Fewer data are available to define risk factors for PNSP among adults. In 1987, a case-control study of adults with bacteremic pneumococcal pneumonia in Spain found that recent use of β-lactam antibiotics and hospitalization during the 3 months prior to the index case of bacteremia were associated with invasive PNSP infection [5].

HIV infection may also be associated with PNSP, although it is not clearly an independent risk factor; in New York City, 71.4% of adults aged 20–44 years with invasive PNSP were also infected with HIV [6]. The overall impact of penicillin nonsusceptibility on outcome of infection has not been established, and β-lactam antibiotics continue to be widely recommended as treatment for pneumococcal pneumonia, although concerns about treatment failures in cases of meningitis due to PNSP have prompted recommendations of alternative antibiotics [7].

We undertook this retrospective study to characterize the epidemiology of PNSP infection or colonization among urban adults who received care at San Francisco General Hospital (SFGH). The study was designed to measure the prevalence of PNSP, to identify risk factors predictive of penicillin nonsusceptibility among patients with *S. pneumoniae*, and to compare the outcomes (lengths of stay, inpatient mortality) among hospitalized patients with PNSP to the outcomes for those with penicillin-susceptible *S. pneumoniae* (PSSP).

**Methods**

All *S. pneumoniae* isolates obtained from adult patients (≥18 years old) at SFGH between 11 August 1994 (the time when penicillin susceptibility testing of all pneumococci was initiated) and 31 December 1996 were identified with use of the microbiology computer database. Isolates were classified as penicillin-susceptible (MIC, <.1 $\mu g/mL$), penicillin–intermediate resistant (MIC, between .1 and 1 $\mu g/mL$), or penicillin–highly resistant
A patient-isolate was defined as that recovered from a positive pneumococcal culture for a single patient in a 30-day time span. Isolates from more than one culture and/or from more than one site within 30 days with identical antibiograms were treated as a single patient-isolate. A patient-episode was defined as an episode of *S. pneumoniae* isolation from any site in a single patient for whom no culture in the previous 30 days had yielded *S. pneumoniae*. Respiratory isolates included those obtained from expectorated sputum, induced sputum, tracheal aspirates, bronchial lavage fluids, and bronchial brush material.

Cases and controls were identified by linking microbiology data to the admissions database for SFGH. In order for a case or control to be eligible for inclusion, the date of admission noted in the microbiology database had to correspond with the date noted in the admissions database. Cases were defined as consecutive inpatients \( \geq 18 \) years of age who were admitted between 11 August 1994 and 31 December 1996 and had one or more cultures yielding PNSP. Controls were defined as consecutive inpatients \( \geq 18 \) years of age who were admitted during the same time period and had one or more cultures yielding PSSP but none yielding PNSP.

For subjects with more than one patient-episode of PNSP or PSSP infection/colonization during the time frame of the study, data from the first admission were included in the analysis of risk factors. Those who had both PSSP and PNSP were included as cases, and data from the first admission involving PNSP were included in the analysis. Of the 637 patients identified from the microbiology database, 161 could not be included as cases or controls; most could not be included because they were outpatients at the time the culture specimens were obtained or because information was missing from the admissions database.

Data relevant to evaluating potential risk factors for infection or colonization with PNSP among cases and controls were obtained from aggregate computerized hospital information system databases (patient registration information, diagnosis descriptions and ICD-9 [International Classification of Diseases, 9th revision] codes, inpatient mortality, and inpatient pharmacy computer database records). The inpatient pharmacy database contained information only from 14 July 1995 forward.

Pneumococcal isolates were screened for penicillin-susceptibility with use of a 1.0-\( \mu \)g oxacillin disk on Mueller-Hinton sheep blood agar. All isolates that were not susceptible by the screening test underwent microdilution MIC testing with use of Mueller-Hinton broth with lysed horse blood. The ATCC 49619 pneumococcus was used for quality control [8, 9]. Most pneumococcal isolates were also tested for erythromycin-susceptibility by means of microdilution with a tray prepared with Mueller-Hinton broth and lysed horse blood. Selected pneumococcal isolates, including most of those that were not susceptible to penicillin, were tested for susceptibility to ceftriaxone, trimethoprim-sulfamethoxazole, and/or tetracycline by means of the same microdilution method.

The \( \chi^2 \) test (or the Fisher’s exact test for variables having expected frequencies \( \leq 5 \)) was used to compare the distribution of discrete variables, and differences were considered significant at \( P \) values \( \leq .05 \). Univariable analyses were performed with Epi Info software (Centers for Disease Control and Prevention [CDC], Atlanta), and multivariable logistic regression analysis was performed with LogXact for Windows software (Cytel Software, Cambridge, MA). A map of the addresses of cases and controls (figure 1) was generated with use of Atlas GIS software (Strategic Mapping, Santa Clara, CA).

### Results

A total of 689 patient-episodes of *S. pneumoniae* infection/colonization occurred among 637 adult patients at SFGH during the time frame of this study. In two instances, two pneumococcal patient-isolates with different penicillin susceptibilities were obtained during a single patient-episode. The proportion of patient-isolates that were not susceptible to penicillin was 14.5% (17/117) in 1994 (4.3% highly resistant), 17.1% (54/316) in 1995 (3.5% highly resistant), and 14.0% (36/258) in 1996 (3.9% highly resistant). MICs of penicillin for all of the strains that were highly resistant were either 2 \( \mu \)g/mL or 4 \( \mu \)g/mL.

A total of 428 of the patient-isolates grew only in respiratory specimens; 90 (21.0%) of these 428 respiratory isolates were not susceptible to penicillin (4.7% were highly resistant). Two hundred thirty-three of the patient-isolates grew in blood cultures. (In some instances, the pneumococcus was also isolated from another site.) Only 15 (6.4%) of these 233 blood isolates were not susceptible to penicillin (2.6% were highly resistant). In five patient-episodes, *S. pneumoniae* was isolated from CSF; in all five episodes, the pneumococcal isolate was susceptible to penicillin. There were 23 isolates from other sites, 21 of which were penicillin-susceptible and 2 of which showed intermediate resistance to penicillin.

The antibiotic profiles for the pneumococcal patient-isolates were examined to evaluate susceptibility to antibiotics other than penicillin. When the isolates were stratified with respect to penicillin-susceptibility (susceptible, intermediate resistant, or highly resistant), the frequency of resistance to tetracycline, ceftriaxone, and trimethoprim-sulfamethoxazole increased with increasing penicillin-resistance (table 1). Note that not all isolates were tested for susceptibility to all antibiotics.

A total of 65 eligible cases with PNSP and 411 eligible controls with PSSP were identified. Among the cases, 48 of 65 (73.8%) had isolates with intermediate resistance, while 17 of 65 (26.2%) had isolates with high-level resistance. The cases and controls did not differ significantly with respect to age, race, gender, homelessness, or year of index culture (table 2). The available home addresses of cases and controls living
within the city of San Francisco were mapped (figure 1). Visual inspection showed that both the cases and the controls were clustered in a neighborhood of San Francisco known as the Tenderloin. This is an area with a large number of low-cost, single-room-occupancy hotels.

In univariable analyses, cases were significantly more likely than controls to have had a prior admission to SFGH within the past 90 days (OR = 2.2; \( P = .03 \)) and to have had prior inpatient treatment at SFGH with a \( \beta \)-lactam antibiotic within the past 90 days (OR = 2.8; \( P = .03 \)). Prior inpatient treatment at SFGH with any class of antibiotics did not reach statistical significance (OR = 2.1; \( P = .10 \)). Infection with HIV/AIDS (as determined by the ICD-9 code for discharges within 90 days after the index episode or any time prior to the index episode, the admission diagnosis description, and/or HIV antibody test result within 90 days after the index diagnosis or any time prior to the index diagnosis) was not associated with PNSP (table 3), nor was a history of alcohol abuse (data not shown).

The number of subjects with ICD-9 codes or admission diagnoses suggestive of other risk factors for invasive pneumococcal resistance to other antimicrobials as a function of penicillin susceptibility. The microbiology laboratory at SFGH routinely tests all pneumococcal isolates for susceptibility to penicillin and erythromycin. PNSP are usually tested for susceptibility to tetracycline, ceftriaxone, and trimethoprim-sulfamethoxazole, while PSSP often are not tested for susceptibility to these additional antibiotics.

<table>
<thead>
<tr>
<th>Pneumococcal isolates</th>
<th>Tetracycline</th>
<th>Erythromycin</th>
<th>Ceftriaxone</th>
<th>Trimethoprim-sulfamethoxazole</th>
<th>( \geq 3 ) Antibiotics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Susceptible to penicillin</td>
<td>9/43 (21)</td>
<td>24/583 (4)</td>
<td>0/44 (0)</td>
<td>21/44 (48)</td>
<td>4/44 (9)</td>
</tr>
<tr>
<td>Intermediately resistant to penicillin</td>
<td>50/79 (63)</td>
<td>45/81 (56)</td>
<td>5/81 (6)</td>
<td>55/81 (68)</td>
<td>34/81 (42)</td>
</tr>
<tr>
<td>Highly resistant to penicillin</td>
<td>21/25 (84)</td>
<td>9/25 (36)</td>
<td>15/25 (60)</td>
<td>24/25 (96)</td>
<td>19/25 (76)</td>
</tr>
</tbody>
</table>

NOTE: PNSP = penicillin-nonsusceptible \( S. \) pneumoniae; PSSP = penicillin-susceptible \( S. \) pneumoniae; SFGH = San Francisco General Hospital.
Table 2. Demographic characteristics of cases and controls.

<table>
<thead>
<tr>
<th></th>
<th>No. (%) of</th>
<th></th>
<th>No. (%) of</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>(n = 65)</td>
<td>(n = 411)</td>
<td>(n = 411)</td>
</tr>
<tr>
<td>Age (y)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>44 ± 14</td>
<td>45 ± 13</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>40</td>
<td>42</td>
<td></td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>28 (43)</td>
<td>161 (39)</td>
<td>.76</td>
</tr>
<tr>
<td>Black</td>
<td>26 (40)</td>
<td>178 (43)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>11 (17)</td>
<td>72 (18)</td>
<td></td>
</tr>
<tr>
<td>Male:female</td>
<td>3.3:1</td>
<td>3.5:1</td>
<td>.99</td>
</tr>
<tr>
<td>Homeless</td>
<td>9 (14)</td>
<td>93 (23)</td>
<td>.15</td>
</tr>
<tr>
<td>Year of index culture</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1994</td>
<td>10 (15)</td>
<td>61 (15)</td>
<td>.94</td>
</tr>
<tr>
<td>1995</td>
<td>33 (51)</td>
<td>202 (49)</td>
<td></td>
</tr>
<tr>
<td>1996</td>
<td>23 (35)</td>
<td>148 (36)</td>
<td></td>
</tr>
</tbody>
</table>

NOTE. Percentages may not add to 100%, secondary to rounding.

Table 4. Sites of positive culture specimens: cases vs. controls.

<table>
<thead>
<tr>
<th></th>
<th>No. (%) of</th>
<th></th>
<th>No. (%) of</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n = 65)</td>
<td>(n = 411)</td>
<td>(n = 411)</td>
</tr>
<tr>
<td>Positive specimen</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory only</td>
<td>55 (84.6%)</td>
<td>236 (57.4%)</td>
<td>.01</td>
</tr>
<tr>
<td>Blood</td>
<td>10 (15.4%)</td>
<td>162 (39.4%)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>0 (0)</td>
<td>13 (3.2%)</td>
<td></td>
</tr>
</tbody>
</table>

NOTE. \( \chi^2 \) P < .001 for site, overall.

Pneumonia, as defined by ICD-9 code and/or admission diagnosis, was less common among cases: 33 of 65 cases (50.8%) met the definition for pneumonia, compared with 283 of 411 controls (68.9%) (OR = .47; P < .01). Cases with pneumonia were also less likely to be bacteremic (7 of 33, 21.2%) than were controls (134 of 283, 47.3%) (OR = .30; P < .01). Overall, 36 of 65 cases (55.4%), vs. 324 of 411 controls (78.8%), were believed to have invasive disease on the basis of a diagnosis of pneumonia and/or isolation of the pneumococcus from a sterile site.

In the final logistic regression model, only prior admission to SFGH within 90 days of the index admission (OR = 2.38; P = .02) and culture-positivity of only a respiratory specimen (OR = 4.24; P < .0001) were independent predictors of PNSP. The decreased likelihood of pneumonia with PNSP almost reached statistical significance (OR = .60; P = .06).

No significant difference in the length of hospital stay among cases and controls was identified. For cases, the mean length of stay was 7.6 days (SD, 9.5 days), and the median was 5 days; for controls, the mean length of stay was 8.5 days (SD, 11.6 days), and the median was 4 days. Bacteremic cases had a mean length of stay of 6.7 days (SD, 5.8 days), and bacteremic controls had a mean length of stay of 7.8 days (SD, 11.1 days). In addition, no difference in inpatient mortality was observed, but the power to detect a difference in this study was very low, given the small number of events. Six case-patients (9.2%) vs. 31 controls (7.5%) died in the hospital (OR = 1.25; P = .82). Of the 10 bacteremic cases, 3 died (30%), whereas 21 of the 162 bacteremic controls died (13.0%) (OR = 2.90; P = .15). The data did demonstrate that pneumococcal bacteremia was associated with higher mortality (OR = 3.63; P < .001), but the relationship is not confounded by penicillin-nonsusceptibility.

Discussion

Over the last several years, surveillance by the CDC has documented a clear increase in the proportion of pneumococci that are penicillin-nonsusceptible [10]. Recent data suggest that nationwide, >30% of S. pneumoniae strains are no longer fully susceptible to penicillin [11]. In any institution, the prevalence of PNSP is relevant to decisions regarding empirical treatment.
of suspected *S. pneumoniae* infections. At SFGH, the prevalence of PNSP did not increase over the relatively brief time span included in this study.

Our data do not demonstrate that infection caused by PNSP adversely affects inpatient mortality. A retrospective study in Spain published in 1987 suggested that mortality was increased among patients with bacteremic pneumonia due to PNSP [5]. However, a larger, prospective study published in 1995 showed no increase in mortality after adjustment for other predictors of poor outcome [12].

A retrospective study of Korean children with invasive pneumococcal disease also showed no difference in mortality between patients with penicillin-nonsusceptible vs. susceptible organisms [13]. Given that an association with PNSP and increased mortality have been difficult to demonstrate, it is not surprising that our study did not show a difference in mortality between cases and controls, as only six inpatient deaths occurred among the cases.

Risk factors for colonization with and infections due to PNSP have been addressed in a number of prior studies, particularly of pediatric patients. The most consistent and strongest risk factor appears to be prior antibiotic exposure [14–17]. In this study, hospitalization within 90 days of index culture was significantly associated with the isolation of PNSP. Inpatient treatment with β-lactam antibiotics at SFGH within 90 days of index culture was associated with the isolation of PNSP in the univariable analysis only. (Note that data were not available for dates earlier than 14 July 1995.)

Prior β-lactam use did not seem to be more associated with PNSP colonization than with invasive disease (or vice versa). With our study design relying on retrospectively obtained computerized information, we were not able to evaluate outpatient antibiotic exposure or inpatient antibiotic exposure at other hospitals as risk factors.

There was a strong correlation between the site of positive pneumococcal culture and the isolation of PNSP. There is at least one previous report that describes a difference in the proportions of PNSP recovered from noninvasive vs. invasive specimens [18]. We also noted a trend toward a decrease in the proportion of cases with pneumonia, although this did not quite reach statistical significance in the multivariable analysis.

Note that one important limitation of this study is that information was available only regarding positive blood cultures; i.e., no data were available regarding blood cultures that were performed but were ultimately negative. It is possible that the cases had fewer blood cultures performed, accounting for their lower rates of bacteremia; however, we have no reason to believe that such a systematic difference occurred.

The possible decrease in pneumonia with PNSP and the decrease in bacteremia suggest that PNSP may be less virulent and/or less invasive than susceptible strains. There are at least two plausible reasons for this association. First, it may be that the particular strains of PNSP at SFGH are coincidentally less virulent. Clonal spread of PNSP has been well described [19, 20], and several pneumococcal serotypes are known to be associated with penicillin-nonsusceptibility [1]. Outbreaks of pneumococcal disease are relatively uncommon but may occur in closed populations, such as a recently described outbreak of multidrug-resistant pneumococcal pneumonia in a nursing home [21]. Therefore, it is possible that at SFGH one or several clones of PNSP may predominate.

Serotyping of some of the pneumococcal isolates included in this case-control study has been performed. Serotypes are known for 8 of the cases (all blood isolates; 4 different serotypes, including 3 of type 23F and 2 with high-level resistance) and 40 controls (39 blood isolates and 1 CSF isolate; 18 different serotypes, including 9 of type 4). Given these limited data, there were no clear differences between the serotypes of the cases and controls, nor could we draw any conclusions about the relative prevalences of vaccine and nonvaccine serotypes.

Second, it is possible that at least some mutations in penicillin-binding proteins that confer penicillin-resistance also affect the organism’s propensity to cause disease. PNSP is clearly very “fit,” given its increasing prevalence in surveillance studies. However, it is possible that in at least some instances, the ability of PNSP to colonize susceptible hosts outweighs its tendency to cause invasive disease. Further research will be needed to address the issues raised by this study.

Acknowledgments

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References


This stamp was issued by the Congo People’s Republic in 1975 to honor Alexander Fleming (1881–1955), who discovered penicillin for which he received the Nobel Prize in Physiology and Medicine in 1945. It illustrates Fleming and a culture plate demonstrating bacterial sensitivity. (From the medical philately collection of Dr. J. N. Shanberge, University of Michigan.)