Invasive Pneumococcal Disease: Clinical Features, Serotypes, and Antimicrobial Resistance Patterns in Cases Involving Patients with and Without Human Immunodeficiency Virus Infection

Renee E. Frankel, Michael Virata, Catherine Hardalo,* Frederick L. Altice, and Gerald Friedland

We reviewed 153 episodes of invasive pneumococcal disease involving 147 hospitalized patients with and without human immunodeficiency virus (HIV) disease to examine and compare epidemiologic and clinical features, capsular serotypes, and antibiotic susceptibility patterns. HIV infection was the most common risk factor for invasive pneumococcal disease. Pneumococcal disease in HIV-infected individuals was characterized by the greater frequency with which pneumonia was the source of bacteremia (90% vs. 63%) (P < .01) and an increased recurrence rate (15% vs. <1%) (P < .01). The overall mortality rate was 12% and did not vary by HIV serostatus. Capsular-type data were available for 149 episodes; 90% of the types were among those found in the polyvalent pneumococcal vaccine. The four most common capsular types causing invasive disease were 14, 6b, 9v, and 22f; capsular type 9v was significantly more common among HIV-infected patients (P < .01). Penicillin-resistant isolates were identified in 7.2% of all cases, and their presence did not vary by HIV status; 20% of isolates from cerebrospinal fluid were resistant. The majority of the resistant isolates were of capsular type 9v. Given the worldwide increase in both HIV and penicillin-resistant pneumococcal infections, better preventative and therapeutic strategies are greatly needed.

Despite the availability of effective antibiotic therapy and a preventative vaccine, disease caused by Streptococcus pneumoniae is a major cause of morbidity and mortality in the United States [1–5]. Most invasive disease occurs at the extremes of age, but population-based studies suggest that the incidence of pneumococcal disease among patients with HIV infection is extremely high, leading to increasing rates of disease in young adults [6–12]. In fact, injection drug use, race, and HIV infection are independent risk factors for pneumococcal disease [9, 13, 14]. In addition, children with AIDS have a particularly increased risk for invasive pneumococcal disease and recurrent invasive disease [15–22]. Finally, penicillin-resistant infections due to S. pneumoniae have also been increasing recently, although information about their incidence in persons with HIV disease is limited.

To further explore these issues, we sought to characterize the epidemiology, clinical features, current serotypes, penicillin-resistance patterns, and recurrence rate of invasive pneumococcal disease in HIV-infected and non-HIV-infected patients in an urban hospital in a community with high rates of drug use and HIV infection.

Methods

The retrospective chart and microbiology review was conducted at Yale–New Haven Hospital, a 900-bed tertiary care medical center that serves southern New England and is the largest community hospital for the city of New Haven, Connecticut. For the 2-year period of 1 January 1992 through 31 December 1993, all patients from whom S. pneumoniae was isolated (from any normally sterile site: blood or CSF) were identified, and their cases were reviewed retrospectively with use of the clinical microbiology records.

Susceptibility to penicillin was tested with use of a 10-μg oxacillin disk in Mueller-Hinton agar supplemented with 5% sheep blood (BBL–Becton Dickinson, Cockeysville, MD). Plates were incubated in ambient air at 35°C for 24 hours and interpreted according to the standards of the National Committee for Clinical Laboratory Standards. Resistance was confirmed by means of microtubule dilution in Mueller-Hinton broth (Sensititre radiometer; Sensititre, Salem, NH).

High-level resistance to penicillin was defined as an MIC of ≥2.0 μg/mL by broth dilution, intermediate resistance was defined as an MIC of 0.12–1.0 μg/mL, and susceptibility was defined as an MIC of ≤0.06 μg/mL or a zone sign around the oxacillin disk of >19 mm [23]. The majority of penicillin-resistant isolates were tested against trimethoprim-sulfamethoxazole (TMP-SMZ), clindamycin, tetracycline, cephalothin, chloramphenicol, and vancomycin by disk diffusion. All isolates were referred for capsular serotyping, which was
performed by the Quellung technique (Eugene Shapiro, M.D., World Health Organization Research Laboratory).

A retrospective chart review with a standardized data-collection instrument was conducted to retrieve relevant clinical information, such as demographic data, date of onset of illness, clinical presentation of invasive pneumococcal disease, outcome, and specific risk factors for pneumococcal disease. Information collected on potential risk factors for invasive pneumococcal disease included a history of tobacco, alcohol, or injection drug use; a history of splenectomy, malignancy, or immunosuppressive treatment with corticosteroids or antineoplastic agents; neutropenia (defined as an absolute neutrophil count of <1,000); known immunoglobulin deficiency; chronic liver disease (as documented by a history of cirrhosis or chronic elevation in hepatic transaminase levels to >5 times the upper limits of normal); chronic pulmonary disease; cardiac disease; and both insulin-dependent and non-insulin-dependent diabetes mellitus.

HIV seropositivity was determined by a positive ELISA and western blot before or during the episode of invasive pneumococcal disease or by a previous clinical diagnosis of AIDS. For the adult patients, if a behavioral risk factor was not mentioned in the medical record, it was systematically recorded that no information was available.

For the HIV-seropositive patients observed as outpatients at Yale-New Haven Hospital, clinic records were reviewed to determine the CDC (Centers for Disease Control and Prevention) stage of infection and previous use (defined as any prescription within 1 month of the episode of invasive disease) of penicillin, cephalosporin, TMP-SMZ, a quinolone, or macrolide antibiotics. Pneumococcal vaccination history was recorded when documented by the outpatient record. CD4+ T-lymphocyte counts were reported for patients for whom counts were performed who were available within 6 months of the episode of invasive pneumococcal infection. Statistical significance of contingency tables was assessed with the Mantel-Haenszel $\chi^2$ test or two-tailed Fisher's exact test.

### Results

#### Clinical Disease

Over the 2-year study period, 153 episodes of invasive pneumococcal disease involving 147 patients were identified; 84 (57%) of the patients were male. Nearly all (98%) of the episodes were of community-acquired disease. There were 106 adults (age, >16 years) and 41 children. The age distribution among those with invasive pneumococcal disease fell into three distinct groups: birth to 2 years, 30–39 years, and ≥60 years (figure 1). The majority (61%) of invasive pneumococcal infections occurring in the fourth decade of life were in patients with documented HIV infection.

Over two-thirds of the adult patients with invasive pneumococcal disease had at least one coexisting medical condition, while only one-third of the pediatric population had an identifiable comorbid condition (table 1). HIV seropositivity was equally distributed among the pediatric and adult populations and was the most common coexisting medical condition in both populations. Of the 147 patients with invasive pneumococcal disease, 33 had documented HIV infection: 25 adults and 8 children. Of the remaining 114 patients without documented HIV infection, 31 were HIV-seronegative, 74 were not tested but lacked identifiable risk factors, and 9 were not tested but had risk factors for HIV infection.

Recent CD4+ lymphocyte counts were available for 23 of the 25 adult patients and for all of the 8 children who were...
known to be HIV-infected. The mean count was 185 cells/mm³ (range, 0–700 cells/mm³) for the adults and 778 cells/mm³ (range, 62–1,820 cells/mm³) for the children (figure 2). Nine patients were taking prophylactic TMP-SMZ at the time of their pneumococcal episode, each of which involved penicillin-susceptible isolates. Because our microbiology laboratory tests only penicillin-resistant strains against other antibiotics, we do not know whether these isolates were resistant to TMP-SMZ.

Of the 147 patients with invasive pneumococcal disease, 53% were white, 33% were black, and 14% were Hispanic. Non-white ethnicity, tobacco use, and injection drug use were more common features among those with documented HIV infection than in those without (P < .01, χ²), while alcohol use was equally common in both groups (table 2). Among the 25 HIV-infected adults, 24 (96%) smoked tobacco and 10 (40%) were active injection-drug users at the time of clinical presentation.

Nineteen individuals died of complications of invasive pneumococcal disease; thus, the overall mortality rate was 12%. The mortality rate was significantly higher among the elderly (age, >70 years) than among all others (29% vs. 10%, P < .01), and it did not vary by HIV serostatus (13% [HIV+] vs. 12%), even when controlled for age. Resistance to penicillin did not influence mortality rates in this study population.

The major clinical syndromes associated with invasive pneumococcal disease were pneumonia (70%), meningitis (10%), otitis media (10%), sinusitis (5%), peritonitis (3%), periorbital cellulitis (3%), and septic arthritis (1%); some patients presented with more than one clinical syndrome (table 3). There were 20 episodes of bacteremia in which the primary focus of infection was not identified. Pneumonia was significantly more common as the source of bacteremia in HIV-infected patients (92% of episodes) than in those without documented HIV infection (63% of episodes) (P < .01). The other major clinical syndromes occurred less frequently, and there were no differences between the two groups when stratified by HIV serostatus.

**Table 2.** Demographic and drug-use characteristics of patients with invasive pneumococcal disease, stratified by HIV status.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>HIV+ (n = 147)</th>
<th>HIV- (n = 147)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (n = 147)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>21/33 (64)</td>
<td>63/114 (55)</td>
</tr>
<tr>
<td>Female</td>
<td>12/33 (36)</td>
<td>51/114 (45)</td>
</tr>
<tr>
<td>Race/ethnicity* (n = 147)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>19/33 (58)</td>
<td>30/114 (26)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>7/33 (21)</td>
<td>13/114 (11)</td>
</tr>
<tr>
<td>White</td>
<td>7/33 (21)</td>
<td>71/114 (62)</td>
</tr>
<tr>
<td>Drug use (n = 106)†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tobacco (≥1 pack per day)*</td>
<td>24/25 (96)</td>
<td>36/78 (46)</td>
</tr>
<tr>
<td>Alcohol</td>
<td>10/25 (40)</td>
<td>19/77 (25)</td>
</tr>
<tr>
<td>Injected drug(s)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Active use (present to &lt;6 mo before admission)</td>
<td>10/25 (40)</td>
<td>2/78 (2)</td>
</tr>
<tr>
<td>Remote use (≥6 mo before admission)</td>
<td>9/25 (36)</td>
<td>2/77 (2)</td>
</tr>
</tbody>
</table>

* P < .001; all other P values were not significant.
† Denominators differ for drug use behavior because such data were reported only for the adult population (age, >16 y).

**Table 3.** Clinical syndromes associated with 153 episodes of pneumococcal bacteremia involving 147 patients.

<table>
<thead>
<tr>
<th>Clinical syndrome*</th>
<th>HIV+ (n = 38)</th>
<th>HIV- (n = 115)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumonia†</td>
<td>35 (92)</td>
<td>73 (63)</td>
</tr>
<tr>
<td>Meningitis</td>
<td>2 (5)</td>
<td>13 (11)</td>
</tr>
<tr>
<td>Primary bacteremia</td>
<td>2 (5)</td>
<td>18 (16)</td>
</tr>
<tr>
<td>Otitis media</td>
<td>4 (10)</td>
<td>11 (10)</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>2 (5)</td>
<td>6 (5)</td>
</tr>
<tr>
<td>Peritonitis</td>
<td>0</td>
<td>4 (3)</td>
</tr>
<tr>
<td>Periorbital cellulitis</td>
<td>0</td>
<td>4 (3)</td>
</tr>
<tr>
<td>Septic arthritis</td>
<td>0</td>
<td>2 (2)</td>
</tr>
</tbody>
</table>

* Some patients presented with >1 clinical syndrome per episode of pneumococcal disease.
† P < .01; all other P values were not significant.

**Capsular Serotypes**

Pneumococcal capsular-serotyping data were available for 149 episodes of invasive pneumococcal disease (table 4). Of these 149 capsular types, 134 (90%) were represented in the current 23-valent pneumococcal vaccine. The six most common capsular types causing invasive pneumococcal disease in patients admitted to Yale–New Haven Hospital were, in descend-
Table 4. Capsular types of pneumococcal isolates recovered during the 149 episodes of invasive pneumococcal disease for which such data were available.

<table>
<thead>
<tr>
<th>Capsular type</th>
<th>HIV+ (n = 38)</th>
<th>HIV- (n = 111)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. (%) of episodes involving indicated patients</td>
<td></td>
</tr>
<tr>
<td>Contained in vaccine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>0</td>
<td>10 (9)</td>
</tr>
<tr>
<td>6b</td>
<td>2 (5)</td>
<td>19 (7)</td>
</tr>
<tr>
<td>9v*</td>
<td>10 (26)</td>
<td>9 (8)</td>
</tr>
<tr>
<td>14</td>
<td>4 (10)</td>
<td>22 (20)</td>
</tr>
<tr>
<td>19f</td>
<td>5 (13)</td>
<td>7 (6)</td>
</tr>
<tr>
<td>22f</td>
<td>2 (5)</td>
<td>11 (10)</td>
</tr>
<tr>
<td>23f</td>
<td>3 (8)</td>
<td>5 (5)</td>
</tr>
<tr>
<td>Other†</td>
<td>9 (23)</td>
<td>17 (15)</td>
</tr>
<tr>
<td>Not contained in vaccine‡</td>
<td>4 (10)</td>
<td>11 (10)</td>
</tr>
</tbody>
</table>

* P < .01; all other P values were not significant.
† 1, 3, 7f, 9n, 10a, 11a, 12c, 18c, 19a, 20a, and 33f.
‡ 6a, 13, 15f, 31, and 33a.

Resistance to Penicillin

Resistance to penicillin was seen in 11 (7.2%) of 153 invasive pneumococcal isolates. Moreover, 3 (20%) of 15 CSF isolates were penicillin-resistant. A total of 10 patients had resistant isolates recovered. Six patients’ strains had high-level penicillin resistance (MIC, ≥2 μg/mL); one of these patients (a 5-year-old boy with HIV infection) was treated for 6 days with intravenous cefuroxime and then for 10 days with oral cefaclor but had recurrent disease (48 days after his initial episode) with a resistant strain of the same serotype. Four patients had moderately resistant isolates recovered (MIC, 0.12–1.0 μg/mL). Patients infected with penicillin-resistant S. pneumoniae were diverse in terms of age, comorbid conditions, HIV serostatus, and major clinical syndrome at presentation (table 5). There were no deaths among the 10 patients with resistant pneumococcal disease. All penicillin-resistant strains were of serotypes covered by the current 23-valent vaccine: 6 were of type 9v, 2 were of type 14, and 1 each were of types 19a, 19f, and 6b. Penicillin-resistant pneumococci were more likely to be of serotype 9v (P < .01) than any other serotype. Pneumococcal infections due to these highly resistant organisms of type 9v clustered in the fall of 1993.

Discussion

In this retrospective chart and microbiology review, we confirmed and further extended observations about invasive pneumococcal disease in the 1990s. This study highlights the importance of advanced HIV disease as an underlying illness—particularly in young adults and young children—the geographic and population-specific serological patterns of infections, the emergence of penicillin resistance in all populations, and the need for better preventative and therapeutic strategies to control invasive pneumococcal infections.

Invasive pneumococcal infections have increased in parallel with the steady rise in AIDS cases in the United States [24]. HIV infection has not been demonstrated to increase the carriage rate of S. pneumoniae [25]; however, it greatly increases the rates of invasive pneumococcal disease [7, 11, 26–29]. Some case reports have documented unusual manifestations of pneumococcal infection among HIV-infected individuals [30, 31], but most others have described a presentation similar to that seen in otherwise healthy hosts [8, 11].

In this series, two differences emerged between those with and without documented HIV infection. First, pneumonia was significantly more common as the primary source of bacteremia in HIV-infected patients (92% of episodes) than in patients without documented HIV infection (63% of episodes). Since injection drug use and race are independent risk factors in the development of pneumococcal pneumonia [13, 14], these findings may have been influenced by the high proportion of injection drug users in the population of HIV-infected patients.
in Connecticut [32]. However, the significant number of invasive pneumococcal infections among HIV-infected children argues against intravenous drug use as the sole risk factor for these invasive infections.

Second, patients with HIV infection had a significantly higher rate of recurrence. RID is common in patients with AIDS [6–8, 15, 20, 24, 25, 27, 33]. For the 2 years observed at this single institution, 15% of our HIV-infected patients had RID. While bacterial pneumonia occurs at early stages of HIV infection, the risk for recurrent invasive disease may increase with a decreasing CD4+ T-lymphocyte count [34].

As we devise better strategies for prophylaxis against opportunistic infections, we may expect increased numbers of patients with advanced HIV infection to become at risk for RID. Given our population of patients with advanced HIV disease or AIDS, this recurrence rate is likely higher than would be observed in persons with earlier stages of disease. Conversely, since we did not review the microbiology records of other institutions in the New Haven area, we may have underestimated the recurrence rate in both the HIV-seropositive and HIV-seronegative populations.

More than 90% of the pneumococcal isolates were of capsular types contained in the currently available 23-valent vaccine, a finding similar to those of larger studies of invasive isolates [35–40]. In other series, serotypes of S. pneumoniae isolated from HIV-infected patients with bacteremia have been the same as those isolated from patients without HIV infection. In our study, HIV-infected patients were more likely to have disease due to capsular type 9v than were other patients. Although 9v is a serotype commonly associated with invasive disease [5, 41], it was uncommon in our patients without documented HIV infection. We were unable to identify any epidemiologic links between HIV-infected patients who had invasive infections due to pneumococci of capsular type 9v.

High-level penicillin resistance, especially in our CSF pneumococcal isolates, was higher than reported in a 1991–1992 survey of invasive pneumococcal isolates from hospitals across the United States [42]. Similar to the findings of Breiman and colleagues in that report, our penicillin-resistant isolates also demonstrated resistance to TMP-SMZ. Given the frequent use of TMP-SMZ in empirical therapy for pneumonia and sinusitis in HIV-infected persons, these multidrug-resistant strains are especially alarming. Indeed, this frequent use may underlie the high rates of resistance to both TMP-SMZ and penicillin. Therefore, while use of TMP-SMZ is an effective prophylactic strategy against Pneumocystis carinii pneumonia, it may be an ineffective prophylaxis for pneumococcal disease.

Several studies have provided evidence of the intercontinental spread of drug-resistant clones of serotypes 23f, 6b, and 9L [38, 40, 43–48]. Although we did not test our isolates for clonality, most of our resistant isolates were of serotype 9v. This finding is particularly interesting given the recent report of a ceftriaxone-resistant pneumococcal 9v isolate from the CSF of a patient in Rhode Island, suggesting a possible regional distribution of these resistant isolates [49]. It is therefore important to monitor pneumococcal resistance in various communities in order to recognize similar strains and prevent spread through infection-control techniques and in order to guide empirical therapy.

The occurrence of penicillin-resistant invasive pneumococcal infection in HIV-infected individuals has been described since 1989 [50–52]. More recently, a prospective population-based study in Barcelona examined whether HIV infection was a predisposing condition in the development of penicillin-resistant invasive pneumococcal infections. Such an association was not found. Rather, multivariate analysis showed a statistically significant association between intermittently penicillin-resistant pneumococci and an age of 0–4 years, the presence of
other immunosuppressive underlying diseases, and the previous use of β-lactam antibiotics. Infection with highly penicillin-resistant pneumococci was associated with the previous use of β-lactam antibiotics [53].

Previous studies did not examine the association between HIV serostatus and penicillin-resistant pneumococci [37, 54–57]. During the 2-year period we studied, penicillin-resistant pneumococcal disease did not emerge more frequently in HIV-infected patients. However, it seems likely that if our population continues to have infections with serotype 9v and this serotype is more likely to be resistant, the prevalence of resistant pneumococcal infections in persons with advanced HIV infection will increase in this geographic area.

Therefore, given the increase in both HIV infection and penicillin-resistant pneumococcal infections throughout the world, we anticipate greater therapeutic challenges in the future. First, we believe that young adults in whom invasive pneumococcal disease develops should be offered counseling and testing for HIV infection. An important goal in the care of HIV-infected patients should be the prevention of pneumococcal disease. While Shapiro and colleagues provide compelling evidence that polyvalent pneumococcal vaccine is effective in preventing invasive pneumococcal disease in the immunocompetent host [3], no population-based studies have been published to determine whether vaccination will benefit this population.

While the current 23-valent vaccine may have some protective benefit in this population, antibody response to the present vaccine is suboptimal in infants, toddlers, and immunosuppressed adults [58–61]. Glaser and colleagues demonstrated that treatment with zidovudine improves the response of persons with HIV infection to pneumococcal vaccine [62]. The new pneumococcal conjugate vaccines, which include the serotypes most prevalent in children, have been shown to induce an adequate serological response in children less than 2 years of age.

This new vaccine should be tested in the adult and pediatric HIV-infected populations as well. Until a more immunogenic vaccine becomes widely available, those with documented HIV infection and those at high risk for HIV infection should be vaccinated at the earliest stage of disease with the currently available polyvalent pneumococcal vaccine.

While other investigators have recommended prophylaxis with penicillin for HIV-infected patients who have had an episode of invasive pneumococcal disease [11], increasing penicillin resistance among pneumococcal isolates makes this a less attractive alternative. In areas with low rates of penicillin resistance, penicillin prophylaxis may be reasonable for those at highest risk; however, the global ecology of penicillin resistance may be altered by such interventions. Finally, given the high incidence of penicillin resistance, particularly in cases of bacterial meningitis, it is prudent to use alternative treatment regimens for life-threatening pneumococcal disease until penicillin susceptibility is determined [63].

The limitations of this study include the biases and clinical imprecision of retrospectively collected chart-review data and the possible underdetection of pneumococcal bacteremia as a result of incomplete sampling and the intermittent nature of pneumococcal bacteremia. With regard to the presence of underlying HIV infection, our findings likely underestimate the burden of HIV infection among individuals with invasive pneumococcal disease, since not all patients in this study were tested for HIV infection.

In this hospital-based sample, there is no information on the size of populations at risk for invasive pneumococcal disease; therefore, it is not possible to construct true incidence rates of disease, particularly in relation to underlying medical conditions. Nonetheless, it is likely that although immunosuppressive therapy, malignancy, chronic obstructive pulmonary disease, and liver disease continue to be important underlying illnesses predisposing to invasive pneumococcal infections, HIV infection is now the most common underlying risk factor for invasive pneumococcal infection. Given the worldwide increase in both HIV infection and penicillin-resistant pneumococcal infections, better preventative and therapeutic strategies are greatly needed.

Acknowledgments

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