Invasive Pneumococcal Disease in Patients Infected with HIV: Still a Threat in the Era of Highly Active Antiretroviral Therapy

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We studied all human immunodeficiency virus (HIV)–infected patients with invasive pneumococcal disease who received their diagnosis during 1996–2002 to investigate the incidence of this disease in the highly active antiretroviral therapy era and to study the influence of CD4 lymphocyte count on the clinical presentation and outcome of disease. The overall incidence of invasive pneumococcal disease was 11.3 cases per 100,000 person-years in adult patients without known HIV infection and 677 cases per 100,000 person-years in HIV-infected patients. This incidence remained stable over the study period. Clinical presentation, severity of illness, and number of recurrent episodes were similar in patients with $CD4^+$ cell counts of >200 or ≤200 cells/μL. Patients receiving trimethoprim-sulfamethoxazole (TMP-SMZ) were more likely to present with TMP-SMZ–resistant pneumococci than were those who were not receiving this agent (76.7% vs. 43.6%; $P = .007$). The mortality rate was high (21%).

The rate of invasive pneumococcal disease among patients with AIDS is significantly higher than the rate in age-matched populations [1–5], and recurrent episodes are more common among these persons [1, 6, 7]. Because of this high incidence of pneumococcal infection, 23-valent pneumococcal vaccine is recommended for all HIV-infected patients, especially during the early stages of the disease [8]. Nevertheless, the efficacy of pneumococcal vaccine among HIV-infected patients remains to be determined, and the level of evidence for the recommendation is not very high [9–12].

Most studies demonstrating this high incidence of pneumococcal infection in HIV-infected patients were performed before the era of HAART. It is possible that potent antiretroviral therapy might improve immunological status enough to provide nonspecific protection against pneumococcal disease. Immune reconstitution after initiation of HAART has reduced the incidence of specific AIDS-defining opportunistic infections. Furthermore, some investigators have observed a decrease in the number of episodes of bacterial pneumonia [13] and even a decrease in the incidence of invasive pneumococcal infection [1, 14]. On the basis of these observations, the value of routine pneumococcal vaccination for all HIV-infected patients has been questioned [14].

The current trends in the incidence of pneumococcal disease since the introduction of HAART have not yet been completely defined. This fact prompted us to conduct the present study, which includes all HIV-infected patients with invasive pneumococcal disease treated at our institution from 1996 up to 2002. Our aim was to determine the incidence of this infection and to study the influence of the patients' CD4 lymphocyte count

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on the clinical presentation, severity, and outcome of invasive pneumococcal disease. Our final objective was to determine whether the efforts to assess measures for the prevention of pneumococcal disease are still worthwhile.

PATIENTS AND METHODS

All adult HIV-infected patients (age, ⩾16 years) with invasive pneumococcal disease attended at our hospital from January 1996 to December 2002 were reviewed. The study was performed at the Hospital Universitari Vall d'Hebron in Barcelona, Spain. The patients' records from 1996 to 1999 were reviewed retrospectively, and from 2000 onward, the study was conducted prospectively. All cases of invasive pneumococcal disease occurring in adult patients were introduced in a database. Invasive pneumococcal disease was defined as isolation of *Streptococcus pneumoniae* from a normally sterile site (i.e., blood, CSF, pleural fluid, peritoneal fluid, or joint fluid). During the period of the study, 467 episodes of invasive pneumococcal disease in patients aged ⩾16 years were diagnosed; 70 of them (15%) occurred in 57 HIV-infected patients. For the purpose of the study, we analyzed each episode separately.

The following variables were recorded for each patient: age, sex, previous episodes of invasive pneumococcal infection, pneumococcal vaccination status, predisposing factors for pneumococcal infection other than HIV infection, clinical presentation, pneumonia class (according to the Pneumonia Severity Index), $CD4^+$ lymphocyte count, virus load (when available), trimethoprim-sulfamethoxazole (TMP-SMZ) prophylaxis, antiretroviral therapy, *S. pneumoniae* serotype, antimicrobial susceptibility, in-hospital complications, hospital mortality, and length of hospital stay. $CD4^+$ lymphocyte count and virus load were determined within 3 months before and 1 month after pneumococcal infection.

S. pneumoniae strains were identified by Gram stain, Optochin susceptibility, bile solubility, and latex agglutination testing. Antimicrobial susceptibility was performed on 69 strains by standard dilution in agar or Etest (AB Biodisk), with Mueller-Hinton medium supplemented with 3% horse blood. Susceptibility was defined according to the 2002 NCCLS guidelines [15]. Strains with intermediate and high levels of resistance were considered to be penicillin nonsusceptible. Isolates were serotyped at the Spanish Pneumococcal Reference Laboratory (Instituto de Salud Carlos III, Madrid, Spain) with standard antiserum.

To calculate the annual incidence of invasive pneumococcal disease, the number of HIV-infected patients visited (at least once) per year of observation was retrieved from the medical record system at our hospital. During the study period, the number of HIV-infected patients progressively increased from 1263 in 1996 to 1594 in 2002, a 26% increase. The total of HIV-negative persons has been estimated among 500,000 inhabitants, which is the number of residents in the area of influence of our hospital. The χ^2 test (or Fisher's exact test) was used to compare the distribution of categorical variables, and Student's t test was used for continuous variables. Differences were considered significant at $P < .05$. The strength of association between single prognostic variables and mortality was calculated, as were ORs and their corresponding 95% CIs. Statistical analyses were performed using EpiInfo (Centers for Disease Control and Prevention) and SPSS statistical software.

RESULTS

During the period of 1996–2002, 467 episodes of invasive pneumococcal disease were identified in adults. Seventy (15%) of them were diagnosed in 57 HIV-infected patients. There were 24 episodes of recurrent invasive pneumococcal disease involving 11 patients. In 6 cases, HIV diagnosis was made at the time the patients had the pneumococcal infection. The 70 episodes occurred in 40 men and 17 women, with a mean age ($\pm$SD) of 36.8 $\pm$ 8 years at the moment of pneumococcal diagnosis. Forty-six (81%) of 57 patients were injection drug users. Predisposing factors for pneumococcal infection other than HIV infection were smoking (40 patients), liver cirrhosis (9 patients), alcohol abuse (10 patients), previous splenectomy (3 patients), chronic lung disease (4 patients), solid tumor (1 patient), and lymphoma (1 patient). No patient had received pneumococcal vaccine previously. $CD4^+$ cell count was available in all episodes: 38 (54.3%) had ⩽200 $CD4^+$ lymphocytes/μL and 32 (45.7%) had >200 $CD4^+$ lymphocytes/μL; 7 of them had >500 $CD4^+$ lymphocytes/μL. Virus load was available in 48 episodes and was undetectable in only 8 cases. In 32 (45.7%) of 70 episodes, the diagnosis of AIDS was made before the pneumococcal infection, and in 23 (32.8%) of these episodes, the patients were receiving HAART; in 12 additional episodes, the patients were receiving suboptimal antiretroviral therapy with <3 drugs; and in 35 episodes, patients were not receiving antiretroviral therapy.

The clinical syndromes included bacteremic pneumonia (55 cases), peritonitis (8 cases), and meningitis (7 cases). The 23-valent polysaccharide vaccine serotypes accounted for 83% of isolates. Thirty-six (52%) of 69 strains were penicillin susceptible (MIC, ⩽0.06 μg/mL), 28 (41%) were intermediately resistant (MIC, 0.12–1 μg/mL), and 5 (7%) were highly resistant (MIC, >2 μg/mL).

Figure 1 shows the percentage of patients with invasive pneumococcal disease and HIV infection, and table 1 gives an estimation of the annual incidence over the study period. The overall incidence of invasive pneumococcal disease was 677 episodes per 100,000 person-years in HIV-infected patients and 11.3 episodes per 100,000 person-years in adult patients without known HIV infection. The risk for invasive pneumococcal

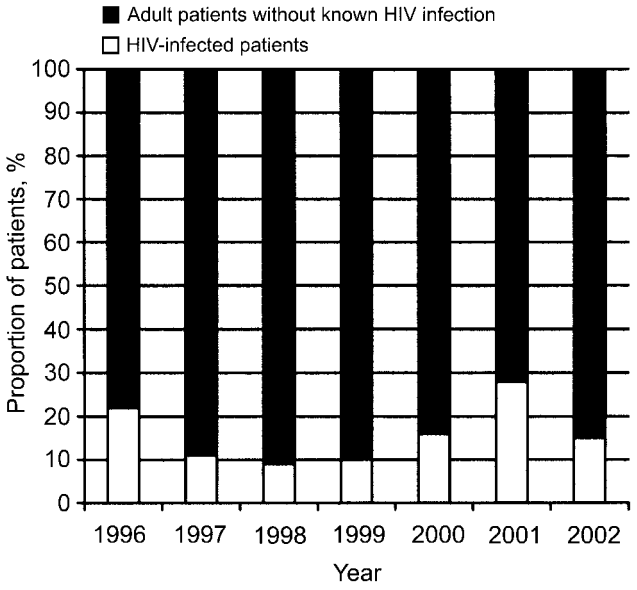

Figure 1. Invasive pneumococcal disease in adult patients with and patients without known HIV infection.

disease was 60 times higher in HIV-infected patients than in the population without known HIV infection. The total number of cases of *Pneumocystis carinii* pneumonia, cerebral toxoplasmosis, and invasive pneumococcal disease diagnosed in our hospital during the study period are summarized in figure 2.

Table 2 shows the influence of $CD4^+$ lymphocyte count on presentation of invasive pneumococcal infection. When patients were compared by $CD4^+$ cell count (>200 or ⩽200 cells/μL) there were no significant differences in clinical presentation, severity of pneumococcal pneumonia, number of recurrent episodes, or penicillin susceptibility. In-hospital mortality was also the same in the 2 groups of patients.

In 30 of the episodes, patients were receiving TMP-SMZ prophylaxis when they received a diagnosis of pneumococcal infection. Comparison between patients who were taking TMP-SMZ and those who were not showed no significant differences in the rate of recurrent infections (20% vs. 15%; $P = .75$), severity of pneumococcal pneumonia as measured by the Pneumonia Severity Index (patients classified as high risk, 44.4% vs. 33.3%; $P = .55$), or mortality (16.7% vs. 25%; $P = .56$). However, we observed that these patients were more likely to present with TMP-SMZ–resistant pneumococci (76.7% vs. 43.6%; $P = .007$) and, although not statistically significant, with penicillin-resistant pneumococci (60% vs. 38.5%; $P = .09$).

Fifteen patients died during hospitalization for pneumococcal infection, making an overall mortality rate of 21%; 7 of the 15 patients who died had >200 $CD4^+$ lymphocytes/μL. Risk factors for increased mortality (table 3) were those related to the severity of the infection such as septic shock (OR, 73.3; 95% CI, 5.06–2421). There was no association between mortality and $CD4^+$ cell count or virus load. Mortality was slightly increased, although not significantly, among patients receiving HAART.

DISCUSSION

The incidence of certain AIDS-related opportunistic infections, such as *P. carinii* pneumonia and cerebral toxoplasmosis, has decreased markedly in our hospital because of this potent antiretroviral therapy, but the number of cases of invasive pneumococcal infection has remained stable. Presently, few data are available regarding the effect of antiretroviral therapy on the risk of pneumococcal disease. Some studies have observed a reduction in the incidence of bacterial pneumonia [13, 16], pneumococcal infection [9], and even invasive pneumococcal disease [1, 14] with the use of antiretroviral therapy. The explanation for this reduction is a reconstitution of T cell and B cell function after the introduction of HAART [17]. All these studies, however, were conducted during the first few years after the introduction of HAART. Our observations also confirmed the tendency for the incidence of invasive pneumococcal disease to decrease during the first 2 years of the study, but this tendency was not apparent from 1999 onward. The risk for invasive pneumococcal disease in our cohort of HIV-infected patients was 60 times higher than in the population without known HIV infection, a risk even higher than that found in one study performed in San Francisco during 1994–1997 [1].

There are some possible explanations for the sustained incidence of pneumococcal infection in our setting. It is known that other factors implicated in host defense besides $CD4^+$ lymphocyte count are impaired during HIV infection. Although humoral dysfunction is among the first immunological sequelae of HIV infection, other factors, such as IgA levels at mucosal surfaces, killing activity of mononuclear cells, and complement bactericidal activity, are defective during HIV infection [2]. All of these factors are involved in the pathogenesis of pneumo-

Table 1. Incidence of invasive pneumococcal infection during 1996–2002 in adult patients without known HIV infection and in HIV-infected patients.

	No. of episodes (cases/100,000 person-years)	
Year	HIV-negative patients	HIV-infected patients
1996	42 (8.4)	12 (950)
1997	49 (9.8)	6 (442)
1998	63 (12.6)	6 (414)
1999	91 (18.2)	10 (668)
2000	54 (10.8)	10 (630)
2001	42 (8.4)	16 (1009)
2002	56 (11.2)	10 (628)
Total	397 (11.3)	70 (677)

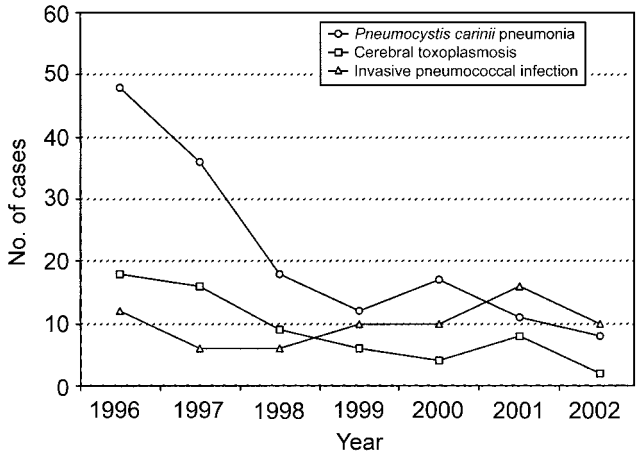

Figure 2. Number of cases of *Pneumocystis carinii* pneumonia, cerebral toxoplasmosis, and invasive pneumococcal infections during 1996–2000 at Hospital Universitari Vall d'Hebron, Barcelona, Spain.

coccal infection. The use of HAART has permitted patients with AIDS to reconstitute their immune system, at least partially; nevertheless, it is not certain when and to what extent the humoral host response is restored [18]. A second reason might be that only 33% of patients in our series were receiving HAART. This is because many patients had only dual antiretroviral therapy in the first years of the study. It is possible that the incidence of invasive pneumococcal disease would have decreased if only patients receiving HAART had been analyzed. Moreover, most of the patients in whom virus load was available had HIV replication (>80 copies/mL), which may impair immune responses to different antigens, as has been recently suggested in a study including patients with *P. carinii* pneumonia and relatively high $CD4^+$ lymphocyte counts [19]. Finally, several risk factors other than HIV infection have been associated with pneumococcal disease, such as intravenous drug use [9, 20, 21], which was present in most of our patients, and other comorbid conditions that were also frequently found among the study population. The presence of such risk factors in the patients under study underlines the higher predisposition to pneumococcal disease among the HIV population.

Pneumococcal infection affects not only HIV-infected patients with low $CD4^+$ lymphocytes, but also those with a $CD4^+$ cell count of >200 cells/μL and even patients with good immunological status. Seven cases of invasive pneumococcal disease in our study occurred in patients with >500 $CD4^+$ lymphocytes. Dworkin et al. [9] also found an increased risk for pneumococcal disease among patients with $CD4^+$ cell counts of 200–499 cells/μL. One limitation of our study is that we did not calculate the incidence of pneumococcal disease separately in patients with >200 or ≤200 $CD4^+$ lymphocytes/μL. Nowadays, a large number of patients are treated with HAART, and many of them have $CD4^+$ cell counts of >200 cells/μL, so it is possible that the incidence of pneumococcal infection was higher in patients with ≤200 $CD4^+$ cells/μL, as has been previously reported [12]. However, the incidence in patients with $CD4^+$ lymphocyte counts of >200 cells/μL is, in our opinion, high enough to promote the use of preventive measures in early stages of the disease.

Severity of illness in cases of bacteremic pneumococcal pneumonia was not linked with $CD4^+$ lymphocyte count, virus load, or a previous AIDS-defining condition. The only factors significantly associated with mortality were those related with the severity of pneumococcal infection (septic shock and intensive care unit admission). In addition, there was a nonsignificant tendency to increased mortality among patients receiving

Table 2. Influence of $CD4^+$ lymphocyte count on invasive pneumococcal infection.

Characteristic	$CD4^+$ lymphocyte count ≤200 cells/μL (n = 38)	$CD4^+$ lymphocyte count >200 cells/μL (n = 32)	P
Pneumonia	30 (78.9)	25 (78.1)	.93
Meningitis	5 (13.2)	2 (6.3)	.44
Peritonitis	3 (7.9)	5 (15.6)	.46
Previous pneumococcal infections[a]	6 (15.8)	6 (18.8)	.76
Pneumonia Severity Index indicating high risk (classes IV or V)	12 (40)	7 (22)	.25
Septic shock[b]	4 (13.3)	2 (8)	.67
Empyema[b]	5 (16.7)	2 (8)	.43
Penicillin-nonsusceptible strain	20 (52.6)	13 (41.9)	.47
Length of stay, mean days ± SD	12.8 ± 11.7	8.1 ± 11	.09
In-hospital mortality	8 (21)	7 (21.9)	.93

NOTE. Data are no. (%) of patients, unless otherwise indicated.

[a] Previous documented episodes of invasive pneumococcal infection.

[b] Only in patients with pneumonia.

Table 3. Univariate analysis of mortality.

Infection	No. of deaths/no. of episodes (%)	OR (95% CI)	*P*
Pneumonia	10/55 (18.2)	0.4 (0.11–1.9)	.28
Meningitis	2/7 (28.6)	1.5 (0.18–10.74)	.64
Peritonitis	3/8 (37.5)	2.5 (0.4–14.74)	.36
Previous pneumococcal infection[a]	1/12 (8.3)	0.3 (0.01–2.52)	.44
Pneumonia Severity Index indicating high risk (classes IV or V)	4/19 (21)	0.5 (0.09–3.06)	.45
Empyema[b]	1/7 (14.3)	0.58 (0.02–5.74)	.62
Septic shock[b]	5/6 (83.3)	73.3 (5.06–2421)	<.0001
Admission to intensive care unit	5/9 (55.6)	6.4 (1.19–35.86)	.018
Penicillin-nonsusceptible strain	9/33 (27.2)	1.9 (0.51–7.02)	.38
Previous AIDS-defining conditions		1.05 (0.29–3.79)	.93
Yes	7/32 (21.9)		
No	8/38 (21.1)		
$CD4^+$ lymphocyte count		0.95 (0.26–3.45)	.93
⩽200 cells/μL	8/38 (21)		
>200 cells/μL	7/32 (21.9)		
Virus load		0.9 (0.12–7.54)	.87
>80 copies/mL	9/40 (22.5)		
<80 copies/mL	2/8 (25)		
TMP-SMZ prophylaxis		1.7 (0.44–6)	.56
No	10/40 (25)		
Yes	5/30 (16.7)		
HAART		0.3 (0.09–1.23)	.07
No	7/47 (14.9)		
Yes	8/23 (34.8)		

NOTE. TMP-SMZ, trimethoprim-sulfamethoxazole.

[a] Previous documented episodes of invasive pneumococcal infection.

[b] Only in patients with pneumonia.

HAART. A previous study at our hospital has shown that the prognosis for purulent meningitis, particularly pneumococcal meningitis, is better for HIV-infected than for HIV-uninfected patients [22]. Other studies have also shown a lower mortality rate among patients with AIDS who have pneumococcal infection. This lower mortality rate has been attributed in part to a decreased inflammatory response to *S. pneumoniae* due to severe immune system impairment [3, 23]. It is possible that the immune system improvement resulting from HAART may favor higher mortality by enhancing that immunological response to pneumococcal infection.

Prophylaxis in pneumococcal infection with the use of antibiotics is currently not advisable because of the risk of developing drug resistance [24, 25]. Although the purpose of our study was not to evaluate the effect of TMP-SMZ on the incidence of pneumococcal infection, we saw that nearly one-half of our patients were receiving it as prophylaxis against *P. carinii* pneumonia when they received a diagnosis of pneumococcal infection. Mortality was not significantly different in patients with or without TMP-SMZ prophylaxis. The only effect of TMP-SMZ was a significantly higher proportion of pneumococci resistant to TMP-SMZ and a nonsignificant trend to a higher level of penicillin nonsusceptibility. In a study performed in France, administration of TMP-SMZ was found to be a risk factor for acquisition of penicillin-resistant pneumococci [25]. This has been explained by the fact that the genes coding TMP-SMZ resistance are physically close to the genes encoding penicillin-binding proteins [26]. Although other studies, like ours, have also shown that isolates obtained from patients receiving TMP-SMZ are more likely to be resistant to this agent [27, 28], a recent population-based surveillance analysis showed that AIDS was not an independent factor for TMP-SMZ nonsusceptibility [29].

The implementation of measures to prevent pneumococcal disease is currently debatable and has been submitted to discussion [14, 30]. Although pneumococcal vaccine is recommended for HIV-infected adolescents and adults who have $CD4^+$ lymphocyte counts of >200 cells/μL, there is limited evidence of its efficacy [9–12]. In areas with low rates of pneumococcal disease, routine administration of pneumococcal vaccine may be questionable [14]. However, in areas with a high incidence, such as ours, and taking into account the high

mortality rate of invasive pneumococcal disease despite improvements in immunologic status with antiretroviral treatment, efforts to assess preventive measures should continue, and pneumococcal vaccine should be offered to HIV-infected patients until new data on its efficacy are available.

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