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Bacteraemic pneumococcal pneumonia: Impact of HIV on clinical presentation and outcome

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Summary *Objectives:* The objectives of this study were to investigate the clinical and laboratory features, hospital course and outcome of patients with bacteraemic pneumococcal pneumonia, comparing HIV with non-HIV patients, as well as HIV patients from different parts of the world.
Methods: This was a multicentre prospective observational study of consecutive adult cases with bacteraemic pneumococcal pneumonia in 10 countries on 6 continents.
Results: A total of 768 cases were recruited, of which 200 were HIV-infected; 166 were from South Africa. Lower age, IV drug use, fewer co-morbid illnesses, and a higher frequency of respiratory symptoms were significantly more likely to occur in HIV patients. The 14-day mortality for the group as a whole was 14.5%, being 16% in the HIV patients and 13.9% in the non-HIV patients (not significant). When adjustments were made for age and severity of illness, HIV patients had significantly higher 14-day mortality with significant trend for increasing 14-day mortality in those with lower CD4 counts. Despite differences in various clinical and laboratory parameters in patients from different parts of the world, on multivariate analysis, when adjusting for regional differences, the HIV-infected patients were still noted to have poorer 14-day mortality.

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Conclusions: This study, in contrast to previous investigations, indicates that there are significant differences in the clinical presentation and outcome of bacteraemic pneumococcal pneumonia when comparing HIV and non-HIV patients.

Introduction

The number of people infected with the human immunodeficiency virus (HIV) is steadily increasing around the world, while the major impact is in Africa.[1–4] Pulmonary diseases, and in particular respiratory tract infections, are a major cause of significant morbidity and mortality in HIV patients.[5] Bacterial pneumonia has been noted to be the most serious lower respiratory tract infection in HIV patients compared with non-HIV patients.[5–8] Furthermore, *Streptococcus pneumoniae* is recognized as the commonest cause of bacterial pneumonia in HIV patients, occurring with a significantly higher rate of bacteraemic infections.[8–13]

Yet there are relatively few clinical studies that have compared the demographic, clinical and laboratory features, hospital course and outcome in HIV versus non-HIV patients, particularly in the setting of invasive pneumococcal disease associated with pneumonia alone.[14–16] The few studies that have been performed were mainly retrospective in design, conducted at a single institution or involved a relatively small number of subjects (49–112 patients).[14–16]

The objectives of the current study were to undertake a global investigation of the demographic, clinical, and laboratory features, the microbiology, the hospital course and outcome of patients with bacteraemic pneumococcal pneumonia, comparing HIV versus non-HIV patients and to determine whether there were any differences in these parameters when comparing HIV-infected patients from different parts of the world.

Methods

In a prospective, multicentre, observational study, conducted previously, 844 consecutive adult patients admitted to hospital with pneumococcal bacteraemia were enrolled between December 1, 1998 and December 31, 2000.[17] Patients were from 21 hospitals in 10 countries and 6 continents. Institutional review board approval was obtained in accordance with local requirements. Patients were observed for at least 14 days after the first blood culture, or longer if the patient remained in hospital.

Patients enrolled from that study for the current investigation were 15 years or older, with at least 1 blood culture positive for *S. pneumoniae* together with radiologically confirmed pneumonia. Patients with confirmed or suspected meningitis were excluded. A wide range of demographic, clinical, and laboratory data were recorded in each patients, as described previously.[17] The antimicrobial susceptibility of all isolates was re-tested and confirmed in a single reference laboratory.

Severity of illness at onset was calculated using the Pitt bacteraemia score, which is of particular value in bacteraemic infections, with a value ≥ 4 being designated as a severe infection, as described previously.[17,18] Briefly, the Pitt bacteraemia score was calculated using the following criteria: (i) oral temperature: 2 points for temperature $\leq 35\,^{\circ}C$, or $\geq 40\,^{\circ}C$, 1 point for temperature of 35.1–36.0 °C, or 39.0–39.9 °C, and 0 points for temperature 36.1–38.9 °C; (ii) hypotension: 2 points for an acute hypotensive event with decreases in systolic and diastolic blood pressure of >30 and >20 mmHg, respectively, use of intravenous vasopressor agents or systolic blood pressure < 90 mmHg; (iii) 2 points for receipt of mechanical ventilation; (iv) 4 points for cardiac arrest; and (v) mental status: alert, 0 points, disorientated 1 point, stuporous, 2 points, and comatose 4 points.

Treatment and outcome measures evaluated included duration of fever, need for admission to the intensive care unit and/or mechanical ventilation, number of days from the positive blood culture to hospital discharge and outcome (overall study outcome and/or outcome at 14 days).

The demographic, clinical, and laboratory features, microbiology, hospital course and outcome for the HIV patients were compared with non-HIV patients. Thereafter the same parameters were analyzed in HIV patients alone, comparing South African patients with patients from the rest of the world.

Statistics

Stata (Intercooled version 7.0, College Station, TX) was used for statistical analysis. Differences in categorical variables were calculated using the 2-sided Fisher's exact test. Continuous variables were analyzed using the Mann–Whitney *U* test. A *p*-value of <0.05 was considered to be significant. A logistic model was used to adjust for the effects of multiple factors, including the possible impact of the South African HIV cases, on the outcome. The model was tested for interactions between the main effects.

Results

Demographic and clinical presentations of the patients stratified by HIV status

A total of 844 cases were recruited for the original study (Table 1). After exclusion of those cases who did not have pneumonia, had co-existing meningitis, or whose HIV status was unknown, 768 remained. Of the 200 patients who were HIV-seropositive, 166 were from South Africa (83%), 10 from the United States, 8 from Brazil, 7 from Spain, 6 from Sweden, and 3 from France.

Table 1 Demographic and clinical characteristics of the patients stratified by HIV status

Variables[a]	HIV positive, $n = 200$ (%)[b]	HIV negative, $n = 568$ (%)[b]	Percent HIV positive	Significance (p-value)
Gender				
Male	111 (55.8%)	326 (57.6%)	25.4	NS
Female	88	240	26.8	
Age (years)				
N	193	550		<0.001
Mean ± SE	33.2 ± 0.62	59.9 ± 0.86		
Median	32.0	62.0		
Age ≥ 65 years				
Yes	1 (0.5%)	243 (44.2%)	0.41	<0.0001
No	192	307	38.5	
Smoker				
Yes	80 (44.2%)	247 (46.3%)	24.5	NS
No	101	286	26.1	
Alcohol use				
Yes	16 (16.0%)	69 (12.1%)	18.8	NS
No	84	499	26.9	
IV drug use				
Yes	15 (15.0%)	10 (1.8%)	60.0	<0.0002
No	85	558	24.9	
Prior history of pneumonia				
Yes	12 (6.3%)	16 (2.9%)	42.9	NS (0.05)
No	180	539	25.0	
Country of origin[b]				
Brazil	8 (4.0%)	21 (3.7%)		
France	3 (1.5%)	18 (3.2%)		
South Africa	166 (83.0%)	54 (9.5%)		
Spain	7 (3.5%)	83 (14.6%)		
Sweden	6 (3.0%)	90 (15.8%)		
USA	10 (5.0%)	90 (15.8%)		

HIV = human immunodeficiency virus; IV = intravenous; and NS = not significant ($p \geq 0.05$).
Young age, IV drug use, and prior history of pneumonia were independent variables associated with HIV seropositivity.
[a] Not all patients had measurements for all variables; tables depict mainly variables showing significant differences between the 2 groups of patients; 2-sided Fisher's exact test.
[b] Percent in brackets refers to what percent those patients contributed to the HIV positive or negative groups respectively; there were no HIV cases among the Hong Kong (31 cases), New Zealand (95), Taiwan (42), or Argentinian (44) cohorts.

HIV patients were significantly younger; only 1 HIV patient was older than 65 years, compared to 44.2% in the non-HIV patients (Table 1). HIV patients were significantly more likely to be intravenous drug users (15% versus 1.8% of non-HIV patients; $p < 0.0002$). More HIV cases had a history of prior pneumonia, but this difference did not reach statistical significance ($p = 0.05$).

On multivariate analysis only younger age, IV drug use, and prior history of pneumonia were independent variables associated with HIV-seropositivity.

Comparisons of the same parameters in HIV positive and negative cases was carried out for the South African cases alone and then for those cases from the rest of the world alone. In both groups of comparisons the younger age was found among the HIV cases ($p < 0.0001$), IVI drug abuse was most common in the HIV cases not from South Africa, and more prior pneumonia and antibiotic use was mainly among the HIV cases not from South Africa.

Underlying co-morbid conditions or treatment in patients stratified by HIV status

Co-morbid illnesses were significantly less common in HIV patients compared with non-HIV patients (Table 2). While none of the HIV patients were receiving treatment with corticosteroids or insulin for underlying co-morbid conditions, a significant number of the non-HIV patients were.

On multivariate analysis heart disease, renal disease, lung disease, malignancy (including hematologic malignancy), and diabetes mellitus were independent variables associated with HIV-seronegativity.

Table 2 Underlying co-morbid conditions or treatment in the patients stratified by HIV status

Variables[a]	HIV positive, $n = 200$ (%)	HIV negative, $n = 568$ (%)	Percent HIV positive	Significance (p-value)[b]
Heart disease				
Yes	5 (2.5%)	159 (28.0%)	3.1	<0.0001
No	194	408	32.2	
Renal failure				
Yes	2 (1.0%)	55 (9.8%)	3.5	<0.0001
No	191	509	27.3	
Lung disease				
Yes	22 (11.4%)	136 (24.1%)	13.9	<0.0002
No	171	428	28.6	
COPD				
Yes	1 (0.5%)	95 (17.0%)	1.0	<0.0001
No	189	463	29.0	
Hem malignancy				
Yes	2 (1.0%)	44 (7.8%)	4.4	<0.0005
No	191	518	26.9	
Other malignancy				
Yes	3 (1.6%)	54 (9.6%)	5.3	<0.0002
No	189	506	27.2	
Diabetes mellitus				
Yes	2 (1.0%)	87 (15.4%)	2.3	<0.0001
No	191	478	28.6	
Autoimmune disease				
Yes	1 (0.5%)	17 (3.0%)	5.6	NS (0.05)
No	192	545	74.0	
Liver disease				
Yes	14 (7.1%)	61 (10.8%)	18.7	NS (0.16)
No	183	505	26.6	
Cirrhosis				
Yes	4 (2.2%)	36 (8.8%)	10.0	<0.005
No	176	372	32.1	
Corticosteroid use				
Yes	0 (0%)	68 (12.1%)	0.0	<0.0001
No	193	495	28.1	
Insulin use				
Yes	0 (0%)	29 (5.3%)	0.0	<0.0005
No	191	518	73.1	

COPD = chronic obstructive pulmonary disease; Hem malignancy = hematologic malignancy; HIV = human immunodeficiency virus; and NS = not significant ($p \geq 0.05$).

Heart disease, renal disease, lung disease, malignancy (including hematologic malignancy), and diabetes mellitus were independent variables associated with HIV-seronegativity.

[a] Not all patients had measurements for all variables; table depicts mainly variables showing significant differences between the 2 groups.

[b] 2-sided Fisher's exact test.

Comparisons of the same parameters in HIV positive and negative cases were carried out for the South African cases alone and then for those cases from the rest of the world alone. In both comparison groups, more HIV negative cases were on corticosteroids and more had diabetes mellitus. There were also more underlying co-morbid conditions and/or malignancies among the HIV negative cases from both comparator groups.

Distribution of clinical presentations of the patients stratified by HIV status

Clinical manifestations, other than hypothermia, were significantly more common in HIV patients compared with non-HIV patients (Table 3). Also, in HIV patients, the clinical manifestations tended to be more common and more severe in patients with lower CD4 counts; sputum production, diarrhoea, and hypothermia tended to occur more commonly in patients with lower CD4 counts, while fever tended to be more common in HIV patients with higher CD4 counts. Bilateral pulmonary infiltrates were significantly more common in HIV than in non-HIV patients ($p < 0.0005$). In addition, in the HIV patients, bilateral pulmonary infiltrates were also more frequent in patients with lower CD4 counts.

On multivariate analysis hypothermia was the only independent variable associated with HIV-seronegativity.

Comparisons of the same parameters in HIV positive and negative cases were carried out for the South African cases alone and then for those cases from the rest of the world alone. In both camparison groups the HIV positive patients were more symptomatic.

Laboratory parameters in the patients stratified by HIV status

Among the laboratory measures only the white cell count (mean $\pm$ SE: $12.2 \pm 0.52 \times 10^9$/l versus $16.8 \pm 0.48 \times 10^9$/l; $p < 0.0001$) and the total protein values (9.1 ± 0.17 g/dL versus 6.3 ± 0.11 g/dL; $p < 0.0001$) showed significant differences between the 2 groups of patients, being lower and higher, respectively, in the HIV-seropositive cases.

Antibiotic susceptibility of the isolates stratifies by patients' HIV status

Receipt of prior beta-lactam antibiotic therapy in the past 3 months was less frequent among HIV patients. In addition the pneumococci from the HIV patients were significantly less likely to be antibiotic-resistant compared with pneumococci from non-HIV patients (Table 4).

Treatment, hospital course and outcome of the patients stratified by HIV status

Significantly fewer HIV patients developed ARDS, were admitted to the ICU, or received mechanical ventilation (Table 5). On univariate analysis there appeared to be no significant difference in the duration of fever, or in the 14-day or overall study outcome when comparing HIV and non-HIV patients (Table 5).

Table 3 Distribution of clinical presentations of the patients stratified by HIV status

Variables[a]	HIV positive, $n = 200$ (%)	HIV negative, $n = 568$ (%)	Percent HIV positive	Significance (p-value)[b]
Cough				
Yes	162 (87.1%)	381 (68.9%)	29.8	<0.0001
No	24	172	12.2	
Chest pain				
Yes	128 (68.8%)	219 (40.9%)	36.9	<0.0001
No	58	326	15.1	
Pleuritic pain				
Yes	136 (73.1%)	193 (35.5%)	41.3	<0.0001
No	50	350	12.5	
Sputum production				
Yes	132 (73.3%)	261 (47.4%)	33.6	<0.0001
No	48	290	14.2	
Haemoptysis				
Yes	50 (27.8%)	58 (10.5%)	46.3	<0.0001
No	130	493	20.9	
Rigors				
Yes	116 (63.7%)	245 (44.2%)	32.1	<0.0001
No	66	299	18.1	
Diarrhoea				
Yes	54 (29.0%)	67 (12.1%)	44.6	<0.0001
No	132	486	21.4	
Vomiting				
Yes	64 (34.4%)	120 (21.7%)	34.8	<0.001
No	122	434	21.9	
Headache				
Yes	59 (32.1%)	83 (15.3%)	41.6	<0.0001
No	125	461	21.3	
Bilateral lung involvement				
Yes	70 (37.8%)	120 (23.5%)	36.8	<0.0005
No	115	390	22.8	
Fever				
Yes	168 (85.3%)	448 (80.9%)	27.3	NS (0.07)
No	29	116	20.0	
Hypothermia				
Yes	4 (2.1%)	38 (6.8%)	9.5	<0.02
No	188	517	73.3	

HIV = human immunodeficiency virus; and NS = not significant ($p \geq 0.05$).
Hypothermia was the only independent variable associated with HIV-seronegativity.
[a] Not all subjects had measurements for all variables; table depicts mainly those variables showing significant differences between the 2 groups.
[b] 2-sided Fisher's exact test.

HIV patients were less likely to be severely ill by univariate analysis (Table 5; $p = 0.07$); however, when stratified by age alone, no statistical difference was found for severity of illness between HIV and non-HIV patients ($p = 0.118$ for the youngest quartile of patients, age < 33 years; $p = 0.7$ for ages 34—51 years). But when adjusted for both age and severity of illness, HIV patients actually had a significantly higher 14-day mortality (OR 4.56 [2.1—9.7]; $p < 0.0001$). The higher mortality occurred in critically ill patients. When stratified by the Pitt bacteraemia score, critically ill HIV patients had a 4-fold risk of death when compared to critically ill non-HIV patients (OR 4.0 [1.4—11.6]; $p < 0.02$).

HIV patients who died had a median CD4 count of 111 cells/μl compared with a median of 179 cells/μl in those who survived (NS; $p = 0.05$). Furthermore, when stratifying the HIV patients according to CD4 count, there was a significant trend for increased 14-day mortality in patients with lower CD4 counts ($p < 0.05$).

Distribution of demographic and clinical characteristics of the HIV patients stratified by country of origin

South African HIV patients were more likely to be female and younger, but the patients were less likely to smoke, to consume alcohol, or to be intravenous drug users (Table 6). The mean temperature and likelihood of having fever were lower in the South African patients. Fewer of the South African patients had a previous history of pneumonia, or had a prior history of antibiotic use within the past 3 months. However, the South African cases were more likely to have chest pain. When these same parameters were evaluated in HIV negative patients, comparing South African and non-South African cases, younger age (median 46.5 years versus 64.0 years; $p < 0.0001$), more chest pain (64.4% versus 37.8% of patients; $p < 0.0005$) and less antibiotic use (8.7% versus 22.0%; $p < 0.05$) still characterized the former cases. Comparing South African and non-South African HIV cases, this episode of pneumonia was more likely to represent their first opportunistic infection or first manifestation of possible HIV infection. Only 5 patients had previously received pneumococcal vaccination; 1 from South Africa and 4 from outside South Africa.

The total protein and blood urea levels were higher in the South African HIV cases, whereas the albumin levels were lower. The overall CD4 count of the HIV patients was 119 cells/μl (range 1—859 cells/μl). The levels in the South African patients (median 103 cells/μl (range 1—859 cells/μl)) were lower than that of the non-South African patients (median 194 cells/μl (range 1—853 cells/μl)). Pneumococcal isolates from the South African patients showed considerably less antibiotic resistance than those from the non-South African patients.

No differences between South African versus non-South African HIV patients were found for severity of illness, duration of fever, and mortality (either 14-day or overall). The number of days of hospitalization of South African versus non-South African patients was not significantly different. When South Africa was added to the logistic model (see Methods), no significant effect was seen on 14-day mortality.

Discussion

This is the largest, prospective study of pneumococcal pneumonia comparing HIV and non-HIV patients ever

Table 4 Antibiotic susceptibility of the isolates stratified by patients' HIV status

Variables[a]	HIV positive, $n = 200$ (%)	HIV negative, $n = 568$ (%)	Percent HIV positive	Significance[b] (p-value)
Prior beta-lactam therapy				
Yes	8 (4.7%)	71 (16.2%)	10.1	<0.0001
No	163	366	30.8	
Azithromycin				
Non-susceptible	11(6.1%)	89 (16.4%)	11.0	<0.0005
Susceptible	170	453	27.3	
Clindamycin				
Non-susceptible	12 (6.6%)	75 (13.8%)	13.8	<0.02
Susceptible	169	467	26.6	
Cefotaxime				
Non-susceptible	11 (6.1%)	78 (14.4%)	12.4	<0.005
Susceptible	170	464	26.8	
Trimethoprim–sulfa				
Non-susceptible	58 (31.9%)	145 (26.8%)	28.6	NS
Susceptible	123	397	23.7	
Ceftriaxone				
Non-susceptible	7 (3.8%)	45 (8.3%)	13.5	NS (0.05)
Susceptible	175	497	26.0	
Cefuroxime				
Non-susceptible	20 (11.0%)	95 (17.5%)	17.4	NS (0.05)
Susceptible	161	447	26.5	
Any cephalosporin				
Non-susceptible	20 (11.0%)	97 (17.6%)	17.1	NS (0.05)
Susceptible	162	445	26.7	
Any macrolide				
Non-susceptible	11(6.1%)	99 (17.9%)	10.0	<0.0001
Susceptible	170	443	27.7	

HIV = human immunodeficiency virus; trimethoprim–sulfa = trimethoprim–sulfamethoxazole; and NS = not significant ($p \geq 0.05$).
[a] Not all subjects had measurements for all variables; table depicts mainly those variables that showed significant differences between the 2 groups.
[b] 2-sided Fisher's exact test.

performed. In contrast to previous investigations, it indicates that there are significant differences in the clinical presentation and outcome of bacteraemic pneumococcal pneumonia when comparing HIV and non-HIV patients. There was a significantly higher 14-day mortality in HIV patients, which was related, at least in part, to their level of immunocompromise, as indicated by their CD4 counts.

Compared with non-HIV patients, the HIV patients with bacteraemic pneumococcal pneumonia were younger, as has been described previously[16] (Table 1). A higher incidence of IV drug use in the HIV group was seen but mostly in cases from outside South Africa (Table 1). However, since the use or not of IV drugs was not recorded in a number of the patients the conclusiveness of the significant difference found is uncertain. Nevertheless, intravenous drug use is a well-characterized risk factor for pneumococcal bacteraemia,[19–21] although it is not recognized as a specific indication for pneumococcal vaccination. However, most other co-morbid conditions studied were significantly more common in the non-HIV patients, most likely representing their risk factor(s) for invasive pneumococcal disease in the absence of HIV infection (Table 2).[22,23] In summary, HIV negative patients with bacteraemic pneumococcal pneumonia were older, more infirm and mostly not from Africa.

Previous studies have demonstrated similar clinical features and severity of illness (based on the APACHE II score) when comparing HIV and non-HIV patients with bacteraemic pneumococcal pneumonia.[16] However, in our larger study, other significant associations were noted. Clinical manifestations of pneumonia were more common or more severe in HIV patients (Table 3). Chest pain was also more common; this has been found to be a favorable prognostic sign in studies of community-acquired pneumonia, probably because of the incentive to consult a physician at an earlier stage of illness. While the fact that symptoms were more prominent may be due to the HIV itself it may also be due to other factors, including the fact that the HIV patients were younger and possibly less tolerant of symptoms or because of cultural differences since these patients were mainly of African origin. Interestingly, and possibly supporting the latter contention, when comparing the South African and non-South African HIV negative cases,

Table 5 Treatment, hospital course and outcome of the patients stratified by HIV status

Variables[a]	HIV positive, $n = 200$ (%)	HIV negative, $n = 568$ (%)	Percent HIV positive	Significance (p-value)[b]
Pitt bacteraemia score				
>4	24 (12%)	99 (17%)	27.3	NS (0.07)
≤4	176	469	19.5	
Fever duration (days)				
N	187	512		NS
Mean ± SE	1.8 ± 2.1	1.9 ± 2.2		
Median	1.0	1.0		
Days from positive blood culture to discharge				
n	199	539		<0.0001
Mean ± SE	6.7 ± 8.2	10.3 ± 11.3		
Median	5.0	6.0		
ICU				
Yes	6 (8.4%)	134 (23.7%)	4.3	<0.0001
No	191	431	30.7	
Mechanical ventilation				
Yes	8 (4.1%)	115 (20.2%)	6.5	<0.0001
No	189	453	29.4	
ARDS				
Yes	1 (0.5%)	34 (6.1%)	2.9	<0.001
No	195	524	27.1	
Outcome				
Lived	164 (82.4%)	463 (82.5%)	26.2	NS
Died	35	98	26.3	
Outcome at 14 days				
Lived	168 (84%)	489 (86.1%)	25.6	NS
Died	32	79	28.8	

HIV = human immunodeficiency virus; ICU = intensive care unit; ARDS = acute respiratory distress syndrome; and NS = not significant ($p \geq 0.05$).

[a] Not all patients had measurements for all variables; tables depict mainly variables showing significant differences between the 2 groups of patients.

[b] 2-sided Fisher's exact test.

the former patients were similarly found to be younger and to have more chest pain.

In HIV patients, clinical manifestations tended to be more common in HIV patients with lower CD4 counts. A trend for increased sputum production, diarrhoea, and hypothermia was seen in patients with lower CD4 counts. Fever tended to be more common in HIV patients with higher CD4 counts, presumably because of improved immune response to infection. Hypothermia was more common in HIV negative cases and it would be interesting to speculate whether this may be occurring in elderly patients in our study who were unable to mount a good febrile response in the presence of pneumococcal bacteraemia and/or who are living in colder climates. Despite this increase in symptomatology, HIV patients were less severely ill as defined by the Pitt bacteraemia score than the non-HIV patients, although this difference did not attain statistical significance ($p = 0.07$) (Table 5).

Bilateral pulmonary infiltrates on chest radiograph were more common in the HIV patients than in non-HIV patients. In addition, in HIV patients, bilateral infiltrates tended to occur in those with lower CD4 counts. Multilobar infiltrates were also more common in HIV patients as already documented in a previous study of South African patients.[16] Also, in a study from Malawi of pneumococcal disease,[24] outpatient death was associated, among other features, with multilobar chest signs.

Fewer HIV patients were admitted to the Intensive Care Unit (ICU), developed ARDS, or were mechanically ventilated (Table 5). While it is possible that this may be due to differences in the availability of ICU beds when comparing countries such as South Africa with Europe/USA, even when South African patients (which were by far the largest group of HIV-infected patients) were excluded from the analysis, the same trend was seen for HIV patients in the other countries, although statistical significance was not attained (data not shown). Interestingly, findings of lower frequency of admission to ICU and decreased necessity for intubation and mechanical ventilation in HIV patients were also noted in a recent U.S. study.[23]

Table 6 Distribution of demographic and clinical characteristics of the HIV − patients stratified by country of origin

Variables[a]	SA, $n = 166$ (%)	Not SA, $n = 34$ (%)	Percent SA	Significance[b] (p-value)
Gender				
Male	87 (52.7%)	24 (70.6%)	78.4	NS (0.06)
Female	78	10	88.6	
Age (years)				
n	162	31		<0.0001
Mean ± SE	32.1 ± 8.6	39.2 ± 6.1		
Median				
Smoker				
Yes	55 (34.4%)	25 (80.6%)	68.8	<0.0001
No	95	6	94.1	
Alcohol use				
Yes	8 (4.8%)	8 (23.5%)	50.0	<0.005
No	158	26	85.9	
IV drug use				
Yes	1 (0.6%)	14 (41.2%)	6.7	<0.0001
No	165	20	89.2	
Chest pain				
Yes	115 (75.7%)	13 (38.2%)	89.8	<0.0002
No	37	21	63.8	
Bilateral pulmonary involvement				
Yes	62 (40.5%)	(25.0%)	88.6	NS
No	91	24	79.1	
Prior history of pneumonia				
Yes	5 (3.1%)	7 (20.6%)	41.7	<0.002
No	54	26	85.6	
First opportunistic infection				
Yes	101 (75.4%)	4 (26.7%)	96.2	<0.005
No	33	11	75.0	
Prior antibiotics				
Yes	14 (9.7%)	16 (55.2%)	46.7	<0002
No	131	13	91.0	
Any prior beta-lactam antibiotic				
Yes	1 (0.7%)	7 (24.1%)	12.5	<0002
No	141	22	6.5	
Prior pneumococcal vaccination				
Yes	1 (0.6%)	4 (16.7%)	20.0	<0.002
No	152	24	86.4	
Fever				
Yes	135 (82.8%)	33 (97.1%)	80.4	<0.05
No	28	1	96.6	
Highest temperature (°C)				
n	152	34		<0.005
Mean ± SE	38.4 ± 0.79	39.0 ± 0.79		
Median	38.5	39.0		

SA = South Africa; IV = intravenous; and NS = not significant ($p \geq 0.05$).

[a] Not all subjects had measurement of all variables; table depicts mainly those variables showing significant differences between the 2 groups.

[b] 2-sided Fisher's exact test.

The outcome of the HIV-infected and non-infected cases in the current study appeared similar by univariate analysis, including their duration of fever, 14-day mortality, and overall mortality (Table 5). Similar findings have been reported in previous studies of all cause pneumonia,[25] as well as in the subset of patients with pneumococcal infection.[15,16,23,26,27] The length of hospital stay was also less for the HIV patients in the current study compared to non-HIV patients. While this has been suggested in other studies,[23] as well, the possible reason for this shorter hospital stay in the current study is that patients at the South African Hospital, once considerably improved medically and stable, are stepped down to a feeder hospital and therefore would appear to have been discharged sooner.

However, since increasing age is a consistent risk factor for mortality in pneumococcal pneumonia [17,22] and because of differences in age and severity of illness noted between our HIV and non-HIV patients (Tables 1 and 5), further analysis was performed. When adjusted for age and severity of illness by multivariate analysis, HIV patients were found to have a significantly higher 14-day mortality (OR 4.56 [2.1—9.7]; $p < 0.0001$) in contrast to previous observations.[15,16,23,26,27] The higher mortality occurred in critically ill patients. When stratified by the Pitt bacteraemia score, critically ill HIV patients had a 4-fold risk of death when compared to critically ill non-HIV patients (OR 4.0 [1.4—11.6]; $p < 0.02$).

For HIV patients, the median CD4 count of those patients who died was 111 cells/μl compared with a median of 179 cells/μl in those who survived (NS; $p = 0.05$). When the HIV patients were stratified by CD4 count, a significant trend for increased 14-day mortality in cases with lower CD4 counts was seen ($p < 0.05$).

As noted previously, most of the HIV infections occurred in South African patients. Differences in HIV patients between the South African ($n = 166$) versus non-South African ($n = 34$) patients may have contributed to some of the differences noted overall between the HIV and non-HIV cases (Table 6). The South African patients had slightly more females and were significantly younger than non-South African patients. The younger age may be expected since in South Africa HIV transmission in adults is usually via heterosexual intercourse, affecting those in their sexually active years.[2] These patients were also less likely to smoke, to take alcohol and to be intravenous drug users. Fewer South African HIV patients had a previous history of pneumonia, or recent prior antibiotic use. The current episode of pneumococcal pneumonia was more likely the first opportunistic infection, or first manifestation of HIV infection. This finding has also been noted in U.S. and Spain and for this reason, we agree that young patients presenting with an episode of invasive pneumococcal infection should be screened for co-existing HIV infection.[12,28]

The pneumococci isolated from HIV patients demonstrated significantly less antibiotic resistance than isolates from the non-HIV patients (Table 4). This may be due to the fact that fewer South African patients had been diagnosed as having pneumonia previously and/or received antibiotics in the past 3 months, known risk factors for pneumococcal antibiotic resistance.[29—33] However, it is interesting to note that there was no difference in the resistance rates to co-trimoxazole in the HIV-infected and -uninfected groups and this possibly could be explained by increased use of co-trimoxazole prophylaxis against *Pneumocystis jiroveci* pneumonia in the former group of patients. Despite some differences in therapy, no differences were found between the South African and non-South African patients with regard to the severity of illness, duration of fever, and either 14-day or overall study mortality. Furthermore, when South Africa was added to the regression models (see Methods), no significant effect was seen on the 14-day mortality or length of hospital stay.

A potential limitation of this study may be that the majority of HIV-infected cases were from South Africa. However, when the multivariate analysis model for outcome was adjusted for South Africa, the results remained essentially the same. Also, the study was conducted over a 3-year period and changes in demography and outcome may have occurred over this time period. Lastly, this is a secondary data analysis and information on exposure to antiretroviral therapy was not available. One may speculate that the outcome in adequately treated HIV-infected patients would be improved, as noted by the poor response in patients with lower CD4 cell counts.

However, this is the largest study of patients with bacteraemic pneumococcal pneumonia in which the clinical, laboratory, microbiological and outcome data have been compared in HIV-seropositive and HIV-seronegative cases. The data were prospectively collected and a number of clinical features were included in the data collection and analysis that had not been previously evaluated. In addition it is the only study that has stratified patients by age, severity of illness and CD4 count levels, to control for confounding variables, the analysis of which has indicated that there are indeed important differences in HIV and non-HIV patients, including significant differences in outcome, which have not been previously recognized.

In conclusion, this large study, in contrast to other smaller studies, demonstrated that significant differences in the clinical course and outcome of bacteraemic community-acquired pneumococcal pneumonia existed for HIV versus non-HIV patients. In future epidemiologic investigations, we recommend that an adjustment for severity of illness at the onset of infection be made when assessing opportunistic infections in HIV versus non-HIV patients. When age and severity of illness were taken into account in the current study, HIV patients had significantly increased 14-day mortality as compared to non-HIV patients. This poorer outcome was related, in part, to their level of immunocompromise, as indicated by their CD4 count.

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