Community-acquired lung respiratory infections in HIV-infected patients: microbial aetiology and outcome

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ABSTRACT We describe the aetiology of community-acquired pneumonia (CAP) in HIV-infected patients, risk factors for bacterial or *Pneumocystis jirovecii* CAP and prognostic factors of 30-day mortality.

This was a prospective observational study of 331 consecutive adult CAP cases in HIV-infected patients (January 2007 to July 2012).

128 (39%) patients had $CD4^+$ cell counts <200 per mm^3 and 99 (43%) ha HIV RNA levels <200 copies per mL on antiretroviral therapy. *Streptococcus pneumoniae* was the most frequent microorganism in the group with $CD4^+$ cell counts $\geqslant 200$ per mm^3; *P. jirovecii* was the most frequent microorganism in the group with $CD4^+$ cell counts <200 per mm^3 and in patients with HIV RNA $\geqslant 200$ copies per mL. Predictors of bacterial CAP were: time with symptoms $\leqslant 5$ days (OR 2.6, 95% CI 1.5–4.4), C-reactive protein level $\geqslant 22$ $mg \cdot dL^{-1}$ (OR 4.3, 95% CI 2.3–8.2) and hepatitis C virus co-infection (OR 2.3, 95% CI 1.4–3.9). White blood cell count $\leqslant 4 \times 10^{12}$ per L (OR 3.7, 95% CI 1.2–11.5), lactate dehydrogenase (LDH) level $\geqslant 598$ $U \cdot L^{-1}$ (OR 12.9, 95% CI 4.2–39.7) and multilobar infiltration (OR 5.8, 95% CI 1.9–19.5) were predictors of *P. jirovecii*. Overall 30-day mortality was 7%. Appropriate antibiotic treatment (OR 0.1, 95% CI 0.03–0.4), LDH $\geqslant 598$ $U \cdot L^{-1}$ (OR 6.2, 95% CI 1.8–21.8) and mechanical ventilation (OR 22.0, 95% CI 6.2–78.6) were the variables independently associated with 30-day mortality.

The described predictors may help clinicians to distinguish between bacterial and *P. jirovecii* pneumonia in patients with suspected or confirmed HIV infection.

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Clinical risk factors in HIV patients to distinguish between bacterial and *Pneumocystis jirovecii* pneumonia http://ow.ly/sV2hf

This article has supplementary material available from www.erj.ersjournals.com

Received: Sept 05 2013 | Accepted after revision: Jan 02 2014 | First published online: Feb 13 2014

Support statement: This work was supported by Ciber de Enfermedades Respiratorias (grant CB06/06/0028), 2009 Support to Research Groups of Catalonia 911 and IDIBAPS.

Conflict of interest: None declared.

Introduction

Community-acquired pneumonia (CAP) is a frequent respiratory complication in HIV patients even in the highly active antiretroviral therapy (HAART) era [1–3]. Patients infected with HIV are 25 times more likely to develop pneumonia. The depletion of $CD4^+$ lymphocytes and high levels of HIV RNA in HIV-infected persons occur in parallel to the risk of developing pulmonary infections [4]. It is well known that $CD4^+$ levels <200 cells per mm^3 are a risk factor for *Pneumocystis jirovecii* pneumonia (PCP) [5–7]. However, there is no information regarding HIV RNA levels. A frequent clinical problem in HIV-infected patients is the clinical difficulty in distinguishing between bacterial CAP and PCP. In the most severe cases, clinicians combine antibacterial therapy and *P. jirovecii* coverage until microbiological results are available. The situation is even more difficult when a bronchoalveolar lavage cannot be performed due to respiratory failure. In patients with undiagnosed HIV, *P. jirovecii* may be ignored and, consequently, these patients may not receive adequate empirical therapy. Accordingly, clinical criteria to help clinicians in choosing antimicrobial therapy are needed.

The aims of this study were to describe the clinical and microbial characteristics of consecutive HIV patients with CAP, to describe the associated risk factors for bacterial pneumonia and PCP, and to assess 30-day mortality prognostic factors.

Methods

Study design and patients

This prospective observational study was carried out in the Hospital Clinic, Barcelona, Spain. All consecutive cases of adult patients with HIV infection and CAP between January 2007 and July 2012 were included. CAP was defined as the presence of a new infiltrate on chest radiography together with clinical signs/symptoms suggestive of lower respiratory tract infection. Mycobacterial and fungal infections (other than *P. jirovecii*) were also recorded but not included in the analysis.

Data collection

A series of clinical and biological data were collected on admission and during patients' hospitalization (online supplementary material). HIV tests were performed in all suspected cases (patients with HIV risk factors, or with presumed or confirmed PCP). Secondary PCP prophylaxis was implemented after cure of the current episode of PCP. All surviving patients were visited or contacted by telephone within 30 days of discharge. This study was approved by the Ethics Committees, Hospital Clinic (number 2009/5451). Patient identification remained anonymous and the need for informed consent was waived due to the observational nature of the study.

Definition

The categorical $CD4^+$ cell count was expressed using the cut-offs <200 and $\geqslant 200$ cells per mm^3. The categorical plasma HIV RNA load was expressed using the cut-offs: <200 and $\geqslant 200$ copies per mL. All patients with undetectable HIV RNA (<200 copies per mL) were on effective HAART. ''Late presenters'' were considered those patients presenting pneumonia with a $CD4^+$ count <350 cells per mm^3 at the time of HIV diagnosis [8].

Appropriateness of empirical antibiotic treatment in all patients was defined according to Infectious Disease Society of America/American Thoracic Society guidelines [9].

Microbiological evaluation

Microbiological investigation was performed on sputum, urine, two blood samples and nasopharyngeal swabs (online supplementary material). Pleural puncture, tracheobronchial aspirates and bronchoalveolar lavage fluid, when available, were collected for Gram, Ziehl–Nielsen, May–Grünwald–Giemsa and Gomori methenamine silver stains, and for cultures of bacterial, fungal and mycobacterial pathogens.

Sputum and blood samples were obtained for bacterial culture before start of antibiotic therapy in the emergency department. Nasopharyngeal swabs for respiratory virus detection and urine samples for *Streptococcus pneumoniae* and *Legionella pneumophila* antigen detection were obtained within 24 h of hospital admission. Blood samples for serology of atypical pathogens and respiratory virus were performed at admission and 4–6 weeks thereafter (online supplementary material).

For the diagnosis of *P. jirovecii* infection we used Gomori methenamine silver stain in respiratory samples. Viral load was determined by Versant HIV-1 RNA 1.0 kPCR (Siemens Diagnostics, Munich, Germany) (lower limit of quantification: 37 copies per mL; upper limit of quantification: 11 000 000 copies per mL) (lower limit of quantification in the period 2007–2009: <50 copies per mL; 2010–2012: <37 copies per mL).

Statistical analysis

Data are presented as n (%) for categorical variables and median (interquartile range (IQR)) for continuous variables with non-normal distribution or mean±SD for those with normal distribution. Categorical variables were compared using the Chi-squared test or Fisher's exact test. Univariate and multivariate logistic regression analyses were performed to identify variables predictive of 30-day mortality (dependent variable). Variables that showed a significant result in the univariate analysis ($p<0.1$) were included in the multivariate logistic regression backward stepwise model. Also, univariate and two multivariate logistic regression models were performed to predict bacterial CAP and PCP, respectively. Highly correlated variables were excluded from multivariate analyses. The Hosmer–Lemeshow goodness-of-fit test was performed to assess the overall fit of the model [10]. The level of significance was set at $p=0.05$ (two-tailed). All analyses were performed using SPSS Statistics 18.0 (IBM, Armonk, NY, USA).

Results

General patient characteristics

During the study period (January 2007 to July 2012), a total of 1985 patients with CAP were admitted to our hospital; 1654 were not HIV infected and were excluded. Our study cohort consisted of 331 (17%) HIV-infected patients hospitalised with a diagnosis of CAP; all these patients were infected by HIV-1. During the same study period, 30 cases of pulmonary tuberculosis and seven fungal respiratory infections (four histoplasmoses, two cryptococcoses and one aspergillosis) were recorded as community-acquired infections in HIV-infected patients but they were not included in our analysis. The main clinical characteristics of the study population are summarised in table 1.

There were 243 (73%) males with a mean±SD age of 42.1±9.5 years. A total of 278 (84%) patients admitted were Spanish and 53 (16%) were from other countries. 320 (97%) patients were hospitalised (63 (19%) in intensive care unit (ICU)) and eight (2%) were treated as outpatients. 59 (18%) patients had received previous antibiotic treatment and 134 (41%) patients received cotrimoxazole as PCP prophylaxis.

HIV infection had been diagnosed prior to hospital admission in 274 (83%) patients and 170 (51%) were on HAART. 57 (17%) patients were diagnosed with HIV infection during the pneumonia episode (within the first 5 days after admission) and were predominantly late presenters (n=46, 81%) and more likely to suffer a *P. jirovecii* infection in comparison with those diagnosed of HIV before pneumonia (35% *versus* 8%) (table 2).

The majority of pulmonary infiltrates (n=225, 68%) were lobar alveolar opacities, followed by interstitial (n=94, 28%) and mixed alveolar–interstitial (n=12, 4%) patterns. Most pneumonia episodes were confined to one lobe (n=198, 60%) and the lower lobes were predominantly affected. Pleural effusion was present in 35 (11%) cases and empyema in eight (2%) cases, while cavitations were described in six (2%) cases.

140 (42%) patients were co-infected with hepatitis C virus (HCV) and 31 (9%) with hepatitis B virus.

The mean±SD $CD4^+$ cell count was 281.3±248.3 per mm^3 (median 240 cells per mm^3, IQR 69–400 cells per mm^3). 128 (39%) patients had $CD4^+$ cell counts <200 per mm^3. The mean HIV RNA level was 236 108±905 528 copies per mL (median 10 300 copies per mL, IQR 61–161 000 copies per mL). 99 (30%) patients had HIV RNA levels <200 copies per mL.

An aetiological diagnosis was achieved in 227 (69%) cases. Monomicrobial infection was detected in 189 (83%) cases and polymicrobial in 38 (17%) cases. The most frequently identified pathogens were *S. pneumoniae* (n=100, 30%; more frequent among patients diagnosed with HIV prior to pneumonia), *P. jirovecii* (n=42, 13%; more frequent among patients diagnosed with HIV during hospitalisation), mixed aetiology (n=38, 11%), respiratory viruses (18, 5%), *Haemophilus influenzae* (n=7, 2%) and *Staphylococcus aureus* (n=6, 2%) (fig. 1 and table 2).

Several differences in radiological features between pneumonias with different aetiological microorganism were observed (online supplementary table 3). *P. jirovecii* and respiratory viruses were the most frequently identified pathogens in cases of the interstitial pattern ($p<0.001$ each) and *S. pneumoniae* in the alveolar pattern ($p<0.001$). Multilobar involvement was more often associated with *S. pneumoniae* ($p=0.025$), *P. jirovecci* ($p<0.001$) and *S. aureus* cases ($p=0.030$). Pleural effusion was more frequent in pneumococcal pneumonia (37%) than for other aetiologies, although this difference was not significant. *S. aureus* was detected in 50% of all cases of pulmonary cavitations.

Only five (5%) out of 100 cases of pneumococcal pneumonia had received the pneumococcal vaccine in the previous five years.

Among the 42 patients with PCP diagnosis, 40 were started on HAART (95%). Six patients died and two of them did not receive HAART therapy. The median (IQR) time from admission to HAART therapy among

DOI: 10.1183/09031936.00155813

TABLE 1 Baseline characteristics of the whole population and of subgroups according to the time of HIV diagnosis

Variables	Total population	HIV diagnosis prior to hospitalisation	HIV diagnosis during hospitalisation	p-value[#]
Subjects n	331	274	57	
Demographics				
Age years mean ± SD	42.1 ± 9.5	42.7 ± 9.1	39.4 ± 10.7	**0.017**
Males	243 (73.4)	193 (70.4)	50 (87.7)	**0.007**
Current smoking	220 (66.9)	192 (70.6)	28 (49.1)	**0.002**
Current alcohol abuse	87 (26.5)	73 (26.9)	14 (24.6)	0.72
Previous antibiotic	59 (17.8)	42 (15.3)	17 (29.8)	**0.009**
Influenza vaccine	20 (7.2)	19 (8.4)	1 (2.0)	0.11
Pneumococcal vaccine	17 (6.2)	17 (7.6)	0 (0)	**0.042**
Time with symptoms days median (IQR)	5.0 (3.0–7.0)	5.0 (3.0–7.0)	7.0 (5.0–14.0)	**0.001**
HAART	170 (51.4)	165 (60.2)	5 (8.8)	**<0.001**
Cotrimoxazole prophylaxis	134 (40.5)	130 (47.4)	4 (7.0)	**<0.001**
Co-infection with HCV	140 (42.3)	130 (47.4)	10 (17.5)	**<0.001**
Co-infection with HBV	31 (9.4)	27 (9.9)	4 (7.0)	0.50
Late presenters[¶]	206 (62.2)	160 (58.4)	46 (80.7)	**0.002**
Comorbidity				
Chronic respiratory disease	97 (29.3)	91 (33.2)	6 (10.5)	**0.001**
Chronic cardiovascular disease	9 (2.7)	7 (2.6)	2 (3.5)	0.69
Diabetes mellitus	14 (4.3)	13 (4.8)	1 (1.8)	0.30
Neurological disease	89 (27.1)	82 (30.1)	7 (12.3)	**0.006**
Chronic renal disease	16 (4.8)	15 (5.5)	1 (1.8)	0.23
Chronic liver disease	108 (32.6)	100 (36.5)	8 (14.0)	**0.001**
$CD4^+$ cells per mm^3				**<0.001**
<200	128 (38.7)	86 (31.4)	42 (73.7)	
⩾200	203 (61.3)	188 (68.6)	15 (26.3)	
Plasma HIV RNA copies per mL				**<0.001**
<200	99 (29.9)	96 (35.0)	3 (5.3)	
⩾200	232 (70.1)	178 (65.0)	54 (94.7)	

Data are presented as n (%), unless otherwise stated. Percentages calculated from nonmissing data. IQR: interquartile range; HAART: highly active retroviral therapy; HCV: hepatitis C virus; HBV: hepatitis B virus. [#]: for comparisons between HIV diagnosis prior to and during hospitalisation; [¶]: persons presenting with pneumonia with a $CD4^+$ count <350 cells per mm^3. Bold indicates statistical significance.

TABLE 2 Microbial aetiology in the whole HIV population (n=331) and subgroups according to the time of HIV diagnosis

Microorganisms	Total population	HIV diagnosis prior to hospitalisation	HIV diagnosis during hospitalisation	p-value[#]
Subjects n	331	274	57	
Unknown aetiology	104 (31.4)	91 (33.2)	13 (22.8)	0.12
Streptococcus pneumoniae	100 (30.2)	90 (32.8)	10 (17.5)	**0.022**
Pneumocystis jirovecii	42 (12.7)	22 (8.0)	20 (35.1)	**<0.001**
Mixed aetiology[¶]	38 (11.5)	28 (10.2)	10 (17.5)	0.11
Respiratory viruses[+]	18 (5.4)	18 (6.6)	0 (0)	**0.047**
Haemophilus influenzae	7 (2.1)	6 (2.2)	1 (1.8)	0.84
Staphylococcus aureus	6 (1.8)	6 (2.2)	0 (0)	0.59
Pseudomonas aeruginosa	4 (1.2)	4 (1.5)	0 (0)	>0.99
Legionella pneumophila	3 (0.9)	3 (1.1)	0 (0)	>0.99
Escherichia coli	1 (0.3)	1 (0.4)	0 (0)	>0.99
Klebsiella pneumoniae	1 (0.3)	1 (0.4)	0 (0)	>0.99
Mycoplasma pneumoniae	1 (0.3)	0 (0)	1 (1.8)	0.17
Other[§]	6 (1.8)	4 (1.5)	2 (3.5)	0.28

Data are expressed as n (%), unless otherwise stated. [#]: for comparisons between HIV diagnosis prior to and during hospitalisation; [¶]: *S. pneumoniae* plus influenza virus A, *H. influenzae* plus influenza virus A, *S. pneumoniae* plus adenovirus, *S. pneumoniae* plus rhinovirus, *L. pneumophila* plus rhinovirus or *S. pneumoniae* plus *P. aeruginosa*; [+]: influenza virus A or B, rhinovirus, adenovirus, respiratory syncytial virus, or parainfluenza virus 2 or 3; [§]: *Enterococcus faecalis, Streptococcus sanguis, Streptococcus constellatus, Fusobacterium* or *Streptococcus pyogenes*. Bold indicates statistical significance.

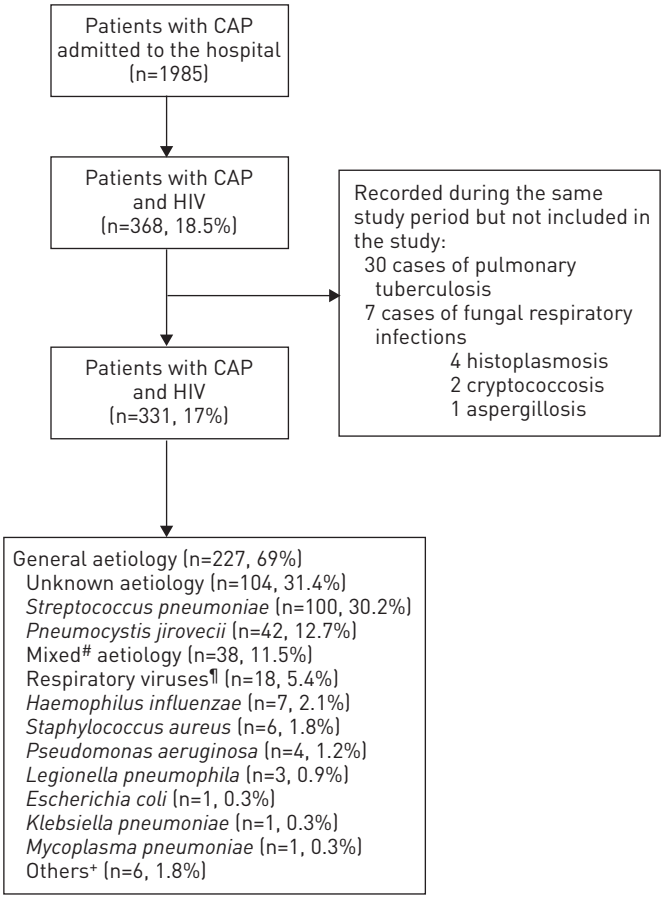

FIGURE 1 Flow chart of general aetiology. CAP: community-acquired pneumonia. #: *Streptococcus pneumoniae* plus influenza virus A, *Haemophilus influenzae* plus influenza virus A, *S. pneumoniae* plus adenovirus, *S. pneumoniae* plus rhinovirus, *Legionella pneumophila* plus rhinovirus or *S. pneumoniae* plus *Pseudomonas aeruginosa*; ¶: influenza virus A or B, rhinovirus, adenovirus, respiratory syncytial virus, or parainfluenza virus 2 or 3; +: *Enterococcus faecalis, Streptococcus sanguis, Streptococcus constellatus, Fusobacterium* or *Streptococcus pyogenes*.

survivors and nonsurvivors patients was 15.5 (10–22.5) and 15.5 (9.5–16) days, respectively (p=0.41). In the second part of the study, HAART therapy was started earlier (14 (8–21) days in 2010–2012 *versus* 16 (14–32) days in 2007–2009, p=0.60).

The median (IQR) length of hospital stay was 7.0 (4.0–13.0) days (table 3). The majority of patients (74%) were classified as low risk (Pneumonia Severity Index class I–III). The most frequent complications were bacteraemia (n=50, 15%) and pleural effusion (n=35, 11%). 63 (19%) patients were admitted to the ICU and 49 (15%) of these required mechanical ventilation. The overall 30-day mortality was 7% and was, globally, slightly higher for infections caused by *H. influenzae* (one (14%) out of seven isolates) and *P. jirovecii* (six (14%) out of 42), while it was only 4% (four out of 100) for pneumococcal infection, 8% (three out of 38) for mixed aetiology, 11% (two out of 18) for respiratory viruses and one fatality case was described for *Escherichia coli* (one isolate).

By comparing patients with PCP with those with bacterial infection, we observed that they were less likely to be current smokers and on chronic treatment with HAART therapy or cotrimoxazole prophylaxis, and to show lower levels of C-reactive protein or leukocyte counts, but described more days of pneumonia-like symptoms prior to hospitalisation, more frequent previous antibiotic therapy, multilobar infiltration on radiography, hypoxaemia, higher lactate dehydrogenase (LDH) levels and worse outcomes (table 4).

Predictors of bacterial CAP

Using receiver operating characteristic (ROC) analysis, the optimal cut-point for C-reactive protein level was 22 $mg \cdot dL^{-1}$, with 35% sensitivity, 87% specificity, 71% predictive positive value, 60% predictive negative value, positive likelihood ratio 2.75 and negative likelihood ratio 0.75, with area under the curve (AUC) 0.65 (95% CI 0.58–0.71), and for LDH was 598 $U \cdot L^{-1}$, with 80% sensitivity, 37% specificity, 54%

DOI: 10.1183/09031936.00155813

TABLE 3 Clinical presentation and outcomes

Variables	Total population	HIV diagnosis prior to hospitalisation	HIV diagnosis during hospitalisation	p-value#
Subjects n	331	274	57	
Laboratory findings				
Creatinine mg·dL^{-1}	0.9 (0.8–1.2)	0.9 (0.8–1.2)	1.0 (0.8–1.4)	0.18
⩾1.5	54 (16.4)	41 (15.0)	13 (23.2)	0.13
C-reactive protein mg·dL^{-1}	11.3 (5.0–21.0)	12.1 (5.1–21.6)	9.0 (4.0–19.0)	0.32
⩾12	147 (49.2)	128 (51.2)	19 (38.8)	0.39
⩾22	69 (23.1)	60 (24.0)	9 (18.4)	0.11
WBCs $\times 10^9$ per L	8255 (5150–11 850)	8850 (5400–11 995)	7000 (4650–10 755)	0.065
>4000	277 (84.5)	232 (85.3)	45 (80.4)	0.35
Platelets $\times 10^9$ per L	207.0 (136.0–300.0)	203.5 (135.5–289.5)	245.0 (151.0–339.0)	0.52
⩾400	16 (7.5)	15 (8.5)	1 (2.7)	0.22
LDH U·L^{-1}	400.0 (337.0–657.0)	347.5 (327.0–545.0)	670.0 (409.0–935.0)	**<0.001**
⩾598	95 (28.7)	61 (22.3)	34 (59.6)	**<0.001**
Oxygen saturation <92%	50 (36.8)	41 (35.3)	9 (45.0)	0.41
Pa_{O_2}/FI_{O_2} <250	59 (29.8)	49 (30.1)	10 (28.6)	0.86
PSI class IV–V	86 (26.3)	71 (26.1)	15 (27.3)	0.86
Multilobar infiltration	133 (40.2)	101 (36.9)	32 (56.1)	**0.007**
Bacteraemia	50 (15.2)	41 (15.0)	9 (15.8)	0.88
Pleural effusion	35 (10.6)	31 (11.3)	4 (7.0)	0.34
ICU admission	63 (19.0)	46 (16.8)	17 (29.8)	**0.023**
Mechanical ventilation	49 (15.4)	43 (16.3)	6 (10.9)	0.31
Septic shock	22 (6.7)	19 (7)	3 (5.4)	0.65
Length of hospital stay days	7.0 (4.0–13.0)	7.0 (4.0–13.0)	10.0 (5.0–17.0)	**0.045**
30-day mortality	22 (6.6)	19 (6.9)	3 (5.3)	0.65

Data are presented as median (interquartile range) or n (%), unless otherwise stated. Percentages calculated from nonmissing data. WBC: white blood cell; LDH: lactate dehydrogenase; Pa_{O_2}: arterial oxygen tension; FI_{O_2}: inspiratory oxygen fraction; PSI: Pneumonia Severity Index; ICU: intensive care unit. #: for comparisons between HIV diagnosis prior to and during hospitalisation. Bold indicates statistical significance.

predictive positive value, 66% predictive negative value, positive likelihood ratio 1.27 and negative likelihood ratio 0.54, with AUC 0.56 (95% CI 0.50–0.63) (online supplementary fig. 1).

Several variables were significantly associated with bacterial CAP at the univariate logistic regression analysis (table 5). Among these variables, ⩽5 days of symptoms (OR 2.6, 95% CI 1.5–4.4), cotrimoxazole prophylaxis (OR 2.0, 95% CI 1.2–3.4), C-reactive protein level ⩾22 mg·dL^{-1} (OR 4.3, 95% CI 2.3–8.2) and HCV co-infection (OR 2.3, 95% CI 1.4–3.9) were identified as risk factors for bacterial CAP in the multivariate analysis. The goodness-of-fit of the model tested using the Hosmer–Lemeshow test revealed adequate model fit (p=0.89).

Predictors of PCP

There was no association between HAART therapy and CAP aetiology, excepting those patients without HAART therapy that presented higher percentages of PCP (20% *versus* 5%, p<0.001). Only five (12%) patients with PCP received cotrimoxazole therapy. This is because, in most cases, the diagnosis of HIV infection was done at the time of hospital admission or because HIV-infected patients had poor adherence to PCP prophylaxis.

Using ROC analysis, the optimal cut-point for C-reactive protein level was 12 mg·dL^{-1}, with 74% sensitivity, 53% specificity, 19% predictive positive value, 93% predictive negative value, positive likelihood ratio 1.57 and negative likelihood ratio 0.49, with AUC 0.65 (95% CI 0.57–0.73), and for LDH was 598 U·L^{-1}, with 86% sensitivity, 80% specificity, 38% predictive positive value, 97% predictive negative value, positive likelihood ratio 4.20 and negative likelihood ratio 0.18, with AUC 0.84 (95% CI 0.77–0.91) (online supplementary fig. 1).

Several variables were significantly associated with PCP in the univariate and multivariate logistic regression analyses (table 6). Among these variables, we found the following independent predictors for PCP: female sex (OR 0.2, 95% CI 0.1–0.9), current smoking (OR 0.4, 95% CI 0.1–0.9), cotrimoxazole prophylaxis (OR 0.1, 95% CI 0.04–0.5), white blood cell (WBC) count ⩽4×10^{12} per L (OR 3.7, 95% CI 1.2–11.5), LDH

TABLE 4 Characteristics of pneumonia cases stratified by microbial aetiology

Variables	PCP	CAP	p-value
Subjects n	42	289	
Demographics			
Age years mean±SD	38.9±7.9	42.6±9.6	**0.019**
Males	36 (85.7)	207 (71.6)	0.053
Current smoking	17 (40.5)	203 (70.7)	**<0.001**
Current alcohol abuse	7 (16.7)	80 (28.0)	0.12
Prior antibiotic treatment	16 (38.1)	43 (14.9)	**<0.001**
Late presenters#	38 (90.5)	168 (58.1)	**<0.001**
Time with symptoms days	7.0 (6.5–14.5)	5.0 (3.0–7.0)	**<0.001**
HAART	9 (21.4)	161 (55.7)	**<0.001**
Cotrimoxazole prophylaxis	5 (11.9)	129 (44.6)	**<0.001**
Co-infection with HCV	9 (21.4)	131 (45.3)	**0.003**
Co-infection with HBV	2 (4.8)	29 (10.0)	0.27
Diagnosis of HIV infection during hospitalisation	20 (47.6)	37 (12.8)	**<0.001**
Comorbidity			
Chronic respiratory disease	4 (9.5)	93 (32.2)	**0.003**
Chronic cardiovascular disease	0 (0)	9 (3.1)	0.25
Diabetes mellitus	0 (0)	14 (4.9)	0.15
Neurological disease	3 (7.1)	86 (30.0)	**0.002**
Chronic renal disease	2 (4.8)	14 (4.9)	0.98
Chronic liver disease	11 (26.2)	97 (33.6)	0.34
Laboratory findings			
Creatinine mg·dL^{-1}	0.8 (0.7–1.1)	0.9 (0.8–1.2)	**0.019**
⩾1.5	3 (7.1)	51 (17.8)	0.082
C-reactive protein mg·dL^{-1}	7.6 (3.0–12.0)	12.6 (5.3–22.2)	**0.002**
⩾12	10 (25.6)	137 (52.7)	**0.002**
WBCs ×10^9 per L	5050 (3800–7100)	9000 (5700–12 400)	**<0.001**
>4000	26 (61.9)	251 (87.8)	**<0.001**
Platelets ×10^9 per L	252.0 (160.0–371.0)	199.0 (135.0–279.0)	**0.023**
⩾400	4 (10.3)	12 (6.9)	0.47
LDH U·L^{-1}	826.5 (657.0–1151.0)	375.0 (327.0–529.0)	**<0.001**
⩾598	36 (85.7)	59 (20.4)	**<0.001**
Oxygen saturation <92%	11 (61.1)	39 (33.1)	**0.021**
P_{aO_2}/F_{IO_2} <250	9 (37.5)	50 (28.7)	0.38
PSI class IV–V	8 (19.0)	78 (27.4)	0.25
Multilobar infiltrates	36 (85.7)	97 (33.6)	**<0.001**
Bacteraemia	0 (0)	50 (17.4)	**0.003**
ICU admission	11 (26.2)	52 (18.0)	0.21
Mechanical ventilation	8 (19.5)	41 (14.7)	0.43
Length of hospital stay days	10.0 (7.0–17.0)	7.0 (4.0–13.0)	**0.030**
30-day mortality	6 (14.3)	16 (5.5)	**0.033**

Data are presented as n (%) or median (interquartile range), unless otherwise stated. Percentages calculated from non-missing data. PCP: *Pneumocystis jirovecii* pneumonia; HAART: highly active retroviral therapy; HCV: hepatitis C virus; HBV: hepatitis B virus; WBC: white blood cell; LDH: lactate dehydrogenase; P_{aO_2}: arterial oxygen tension; F_{IO_2}: inspiratory oxygen fraction; PSI: Pneumonia Severity Index; ICU: intensive care unit. #: persons presenting for pneumonia with a CD4$^+$ count <350 cells per mm^3.

⩾598 U·L^{-1} (OR 12.9, 95% CI 4.2–39.7) and multilobar infiltration (OR 5.8, 95% CI 1.9–19.5). The model was well calibrated with a p-value in the Hosmer–Lemeshow test 0.21.

The combination of both multilobar involvement and LDH ⩾598 U·L^{-1} for the prediction of PCP had a 76% sensitivity, 89% specificity, 51% predictive positive value, 96% predictive negative value, positive likelihood ratio 7.10 and negative likelihood ratio 0.27.

Mortality and predictors of 30-day mortality

The overall 30-day mortality rate was 7% (n=22). PCP was the most frequent isolate in nonsurvivors and differed from survivors (12% *versus* 27%, p=0.033); the rest of the microorganisms did not differ between survivors and nonsurvivors.

DOI: 10.1183/09031936.00155813

TABLE 5 Significant univariate and multivariate logistic regression analyses of predictors for bacterial community-acquired pneumonia in the HIV population

Variables	Univariate		Multivariate#	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Chronic respiratory disease	1.6 (1.0–2.6)	0.051		
Neurological disease	2.1 (1.3–3.5)	0.003		
Current smoking	1.8 (1.1–2.9)	0.013		
Previous antibiotic	0.5 (0.3–0.9)	0.016		
Time with symptoms ⩽5 days	2.9 (1.8–4.5)	<0.001	2.6 (1.5–4.4)	<0.001
HAART	1.6 (1.0–2.5)	0.031		
Cotrimoxazole prophylaxis	1.9 (1.2–2.9)	0.006	2.0 (1.2–3.4)	0.010
Pleuritic pain	1.6 (1.0–2.4)	0.054		
Altered mental status	3.2 (1.3–7.8)	0.011		
Septic shock	3.0 (1.2–7.9)	0.025		
Acute renal disease	2.4 (1.0–5.8)	0.046		
Creatinine ⩾1.5 mg·dL^{-1}	3.0 (1.6–5.6)	0.001		
C-reactive protein ⩾22 mg·dL^{-1}	3.7 (2.1–6.6)	<0.001	4.3 (2.3–8.2)	<0.001
LDH <598 U·L^{-1}	2.3 (1.4–3.8)	0.001		
Multilobar infiltration	0.6 (0.4–1.0)	0.038		
Pleural effusion	2.6 (1.2–5.4)	0.014		
CD4$^+$ count ⩾200 cells per mm^3	1.9 (1.2–3.1)	0.004		
HIV RNA <200 copies per mL	1.5 (0.9–2.4)	0.087		
Co-infection with HCV	2.1 (1.3–3.2)	0.002	2.3 (1.4–3.9)	0.002
Diagnosis of HIV infection prior to hospital admission	2.1 (1.7–3.9)	0.014		

HAART: highly active antiretroviral therapy; LDH: lactate dehydrogenase; HCV: hepatitis C virus. #: Hosmer–Lemeshow goodness-of-fit test p=0.89.

TABLE 6 Significant univariate and multivariate logistic regression analyses of predictors for *Pneumocystis jirovecii* pneumonia in the HIV population

Variables	Univariate		Multivariate#	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Female sex	0.4 (0.2–1.0)	0.060	0.2 (0.1–0.9)	0.033
Age per 5 years	0.8 (0.6–1.0)	0.019		
Chronic respiratory disease	0.2 (0.1–0.6)	0.005		
Neurological disease	0.2 (0.1–0.6)	0.005		
Current smoking	0.3 (0.1–0.5)	<0.001	0.4 (0.1–0.9)	0.033
Previous antibiotic	3.5 (1.7–7.1)	<0.001		
Time with symptoms >5 days	4.8 (2.1–10.7)	<0.001		
HAART	0.2 (0.1–0.5)	<0.001		
Cotrimoxazole prophylaxis	0.2 (0.1–0.4)	<0.001	0.1 (0.04–0.5)	0.003
Pleuritic pain	0.4 (0.2–0.9)	0.023		
Creatinine <1.5 mg·dL^{-1}	2.8 (0.8–9.4)	0.095		
C-reactive protein <12 mg·dL^{-1}	3.2 (1.5–6.9)	0.002		
WBCs ⩽4000×10^9 per L	4.4 (2.2–9.0)	<0.001	3.7 (1.2–11.5)	0.023
LDH ⩾598 U·L^{-1}	23.4 (9.4–58.1)	<0.001	12.9 (4.2–39.7)	<0.001
Multilobar infiltration	11.9 (4.8–29.2)	<0.001	5.8 (1.9–19.5)	0.002
CD4$^+$ count <200 cells per mm^3	10.5 (4.5–24.6)	<0.001		
HIV RNA ⩾200 copies per mL	10.1 (2.4–42.7)	0.002		
Co-infection with HCV	0.3 (0.2–0.7)	0.005		
Diagnosis of HIV infection during the episode of pneumonia	6.2 (3.1–12.4)	<0.001		

HAART: highly active antiretroviral therapy; WBC: white blood cell; LDH: lactate dehydrogenase; HCV: hepatitis C virus. #: Hosmer–Lemeshow goodness-of-fit test p=0.21.

TABLE 7 Significant univariate and multivariate logistic regression analyses of predictors for 30-day mortality in the HIV population

Variable	Univariate		Multivariate#	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Chronic liver disease	3.3 (1.3–7.9)	0.009		
Cough	0.4 (0.2–1.0)	0.054		
Dyspnoea	2.9 (1.0–8.9)	0.057		
Altered mental status	2.9 (0.9–9.3)	0.075		
Septic shock	9.0 (3.2–25.4)	<0.001		
Creatinine ⩾1.5 mg·dL^{-1}	2.6 (1.0–6.7)	0.050		
C-reactive protein <12 mg·dL^{-1}	2.4 (0.9–6.4)	0.084		
WBCs ⩽4×10^{12} per L	4.4 (1.8–10.8)	0.002		
LDH ⩾598 U·L^{-1}	4.0 (1.6–9.7)	0.002	6.2 (1.8–21.8)	0.005
Multilobar infiltration	3.5 (1.4–8.8)	0.008		
Mechanical ventilation	25.7 (8.8–74.7)	<0.001	22.0 (6.2–78.6)	<0.001
Appropriate antibiotic treatment	0.1 (0.04–0.2)	<0.001	0.1 (0.03–0.4)	<0.001

WBC: white blood cell; LDH: lactate dehydrogenase. #: Hosmer-Lemeshow goodness-of-fit test p=0.48.

Univariate and multivariate logistic regression analyses revealed several variables significantly associated with 30-day mortality (table 7).

The multivariate analysis showed that appropriate antibiotic treatment (OR 0.1, 95% CI 0.03–0.4), LDH ⩾598 U·L^{-1} (OR 6.2, 95% CI 1.8–21.8) and mechanical ventilation (OR 22.0, 95% CI 6.2–78.6) were independently associated with 30-day mortality. The goodness-of-fit of the model tested with the Hosmer–Lemeshow test revealed adequate model fit (p=0.48).

Discussion

The most important findings of our study are: 1) *S. pneumoniae* is the most prevalent isolate in HIV-infected patients with pneumonia, followed by *P. jirovecii* and mixed aetiology; 2) *P. jirovecii* is more frequent than *S. pneumoniae* in patients with <200 CD4$^+$ cells per mm^3 and the inverse is true in patients with detectable plasma HIV RNA load (⩾200 copies per mL); 3) an acute clinical course (⩽5 days), the use of cotrimoxazole prophylaxis, a high level of C-reactive protein (⩾22 mg·dL^{-1}) and HCV co-infection are risk factors for bacterial CAP; 4) lower WBC count (⩽4×10^{12} per L), high serum LDH level (⩾598 U·L^{-1}), multilobar infiltration, female sex, current smoking and the use of cotrimoxazole prophylaxis are factors associated with a higher risk of PCP; and 5) appropriate antibiotic treatment, high level of LDH (⩾598 U·L^{-1}) and, particularly, the need for mechanical ventilation are predictors of 30-day mortality.

In this large series of HIV patients with CAP, we found that 50% were not receiving HAART therapy and 37% of patients had CD4$^+$ counts <200 per mm^3. This is because there was a significant proportion of late presenters (62%) and patients with poor adherence to HAART and PCP prophylaxis.

In addition, a large percentage of patients had respiratory, neurological or hepatic comorbidities. Nevertheless, *S. pneumoniae* was the most frequent microorganism isolated. *P. jirovecii* was the second causal microorganism, thus indicating that we still must consider this microbial aetiology. The third aetiological cause was mixed pneumonia and this mainly included a combination of bacteria plus a respiratory virus. Importantly, we found only four cases of *Pseudomonas aeruginosa* and other multiresistant microorganisms were not isolated. CORDERO *et al.* [11] found that *S. pneumoniae* was the most frequent aetiology, followed by *P. aeruginosa* (20%) and *H. influenzae* (14%). Possibly, the observed discrepancy in the *P. aeruginosa* rate is possibly due to different HIV populations, as the study by CORDERO *et al.* [11] was published more than 12 years ago. In a recent extensive review article [2], *H. influenzae* is quoted as the second bacterial cause in this population while we found only a few cases of this infection.

More recent reports from the EuroSIDA cohort do no report microbial aetiology [12]. The originality of our report is the inclusion of bacterial and *P. jirovecii* causes of CAP together, as we believe this corresponds to the clinical reality when dealing with HIV-infected patients with pulmonary infiltrates admitted to hospital from the community.

By dividing patients according to CD4$^+$ count, we find that *P. jirovecii* was the most frequent microorganism in patients with <200 CD4$^+$ cells per mm^3 (online supplementary table 1), followed by *S. pneumoniae* and

DOI: 10.1183/09031936.00155813

mixed aetiology. These findings are not surprising and in line with other studies describing that HIV-infected patients with low $CD4^+$ counts have a higher chance of suffering a PCP. However, in this population (<200 $CD4^+$ cells per mm^3), we should still consider *S. pneumoniae* and mixed aetiologies, and cover these microorganisms accordingly.

We also stratified patients according to plasma HIV RNA load (online supplementary table 2). Although the level of HIV RNA copies could not discriminate *S. pneumoniae*, *P. jirovecii* was rare in patients on HAART (<200 copies per mL) who were virologically suppressed, regardless their level of $CD4^+$ cell count. This the first study performing this kind of analysis. This observation might be useful for clinicians to guide initial antibiotic treatments in the emergency department.

Despite all these findings, in clinical practice, it is difficult to discriminate between bacterial CAP and PCP, and clinicians often cover both types of microorganisms until microbiological results are available. Among the reasons for this there are surely the lack of information on the immunological status of HIV patients and the clinicians' apprehension of undiagnosed HIV cases. Considering these aspects, it would be useful to have clinical and biological predictors to distinguish between bacterial CAP and PCP, and to support the initial decision on empirical antibiotic therapy while HIV infection is still not clear.

In our study, multivariate analysis showed some predictors of bacterial CAP: acute clinical course ($\leqslant 5$ days), the use of cotrimoxazole prophylaxis, a high level of C-reactive protein ($\geqslant 22$ $mg \cdot dL^{-1}$) and HCV co-infection. Furthermore, we found that female sex, not smoking, the lack of cotrimoxazole prophylaxis, leukopenia, LDH $\geqslant 598$ $U \cdot L^{-1}$ and multilobar infiltration were factors associated with a higher risk of PCP. Among these, the most important factors were serum LDH and multilobar involvement. Previous articles have emphasised the predictive value of serum LDH in PCP. A recent Swiss report [13] found a sensitivity of 100% and a specificity of 58% using LDH >250 $U \cdot L^{-1}$. In our study, the combination of both multilobar involvement and LDH $\geqslant 598$ $U \cdot L^{-1}$ gave very good operational values (76% sensitivity and 89% specificity) and could support the medical decision to empirically cover PCP in the case of a concomitant clinical suspicion of HIV infection. This clinical dilemma may be resolved in the near future with the use of rapid molecular point-of-care microbiological testing.

Interestingly, we found that current or past smoking was independently associated with a lower risk of *P. jirovecii*. A recent report by GORDIN *et al.* [14] found, in a follow-up study, that actively smoking HIV-infected patients who had interrupted HAART had an increased risk of bacterial pneumonia. The effect of smoking on the development of PCP is consistent with data from by SHIVJI *et al.* [15] who showed that *S*-adenosylmethionine, a critical cellular metabolic intermediate necessary for *P. jirovecii* growth, is significantly reduced by nicotine exposure. This finding clearly explains the reduced rate of PCP among smoking AIDS patients [15].

In this study, the observed 30-day mortality was only 7%, while only 63 (19%) patients required ICU admission and 49 (15%) mechanical ventilation. Our recent fatality rate is possibly better than that we expected and clearly driven by PCP, as also shown in a previous multicentre Spanish HIV series (2000–2004) describing an overall mortality rate of 15% for PCP (rising to 80% in patients requiring mechanical ventilation), with very similar ICU (21%) and mechanical ventilation rates (16%) [16]. The mortality in our series dramatically increases with PCP, being more than double that of bacterial CAP (14% *versus* 6%) (table 3). The only three variables independently associated with mortality in the overall HIV population were: appropriate antibiotic treatment (OR 0.1, 95% CI 0.03–0.4); LDH $\geqslant 598$ $U \cdot L^{-1}$ (OR 6.2, 95% CI 1.8–21.8), which was clearly correlated to PCP (table 5); and mechanical ventilation (OR 22.0, 95% CI 6.2–78.6).

Some limitations of our study must be pointed out. First, it included only patients visiting our hospital. Second, the complete diagnostic work-up and microbiological sampling could not be fully applied in all patients. This means that some viral or atypical causes of CAP could have been missed. However, all patients were enrolled in the study prospectively and consecutively, thus lending consistency to our data.

In conclusion, *S. pneumoniae* and *P. jirovecii* are the most frequent microorganisms in HIV patients with CAP. There are several predictors that may help clinicians to distinguish between bacterial and PCP.

Acknowledgements

This study was presented as a part of a thesis in the XI Master of AIDS of the University of Barcelona, Barcelona, Spain. Thanks to M. Tuset Creus (University of Barcelona, Barcelona, Spain) for their support.

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DOI: 10.1183/09031936.00155813