Nosocomial Bacterial Pneumonia in HIV-Infected Patients: Risk Factors for Adverse Outcome and Implications for Rational Empiric Antibiotic Therapy

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Abstract

Background: Nosocomial bacterial pneumonia (NBP) was once considered a common cause of morbidity and mortality among advanced AIDS patients. However, clinical and microbiological characteristics and outcome-associated risk factors in this population are poorly defined.

Patients: We conducted a retrospective study of all HIV-infected patients admitted during the period 1988–2002 at the Infectious Diseases Clinic of Milan, Italy, to determine incidence rate and factors affecting mortality of NBP, and to gather clinical and microbiological findings about the condition.

Results: We identified 120 episodes of NBP among 4,967 admissions of HIV-infected individuals. A reduction of incidence became evident after the introduction of highly active antiretroviral therapy (HAART). The more common causative agents were *Pseudomonas aeruginosa* (33%) *Staphylococcus aureus* (25%) and *Streptococcus pneumoniae* (21%). Methicillin resistance was frequent among staphylococci (65%). The mortality rate of NBP was 25.8%. Non-statistically significant factors associated with shorter survival were: CD4+ count < 10 cells/µl, concomitant lung neoplasm, and complicated roentgenographic picture. Only one factor was significantly associated with lower survival, both in univariate and multivariate analysis: a methicillin-resistant *Staphylococcus* serving as an etiologic agent of pneumonia (RR 4.05; 95% CI, 1.076–15.239; p = 0.039).

Conclusion: A decline in incidence of NBP in HIV-infected individuals was observed after introduction of HAART. *S. aureus* and *P. aeruginosa* were the leading causes of NBP, but frequency of pneumococcal pneumonia was significant. The sole predictor for mortality was methicillin-resistant *Staphylococcus* as a pneumonia-causing agent.

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Introduction

Nosocomial bacterial pneumonia (NBP) is the second most common nosocomial infection found in hospital-wide surveillance studies, and, along with primary bacteremia, is the leading cause of death from hospital-acquired infections. Studies have identified incidence rates of 0.5–1.0 cases per 100 patients and these rates tend to be higher in immunosuppressed patients [1]. Crude mortality rates for NBP of up to 70% have been reported, whereas attributable mortality ranges from 7% to 58%, depending on the underlying diseases [2–4].

Acquired immunodeficiency syndrome (AIDS) was once associated with a high incidence of bacterial pneumonia, but this phenomenon has declined rapidly since the advent of highly active antiretroviral therapy (HAART) [5, 6]; however, among HIV patients with pulmonary complaints, bacterial pneumonia seems more common in the HAART era than in the pre-HAART era [7]. The overall incidence rate of nosocomial infections in HIV-infected subjects is about 8% of the admitted patients, and pneumonia represents 15–35% of overall nosocomial infections [8–10]. Nosocomial pneumonia in the general population, as well as in HIV-infected people, is deemed to be caused by the same pathogens [11]. This assumption, however, is based on data which are often fragmentary, or originate from autopsy series [12].

The object of our study was to review clinical records of all cases of bacterially originating nosocomial pneumonia in HIV-infected patients in our hospital, in order to determine incidence of nosocomial pneumonia, interpret clinical and microbiological findings, and identify factors associated with mortality.

Patients and Methods

We reviewed hospital records and laboratory data of all HIV-infected patients diagnosed with NBP whose bacterial isolations were clinically significant, who were admitted to the University of Milan's Infectious Diseases Clinic during the period between January 1988 and December 2002.

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Current Centers for Disease Control and Prevention (CDC) definitions were used for diagnosing nosocomial pneumonia [13]. In particular, nosocomial pneumonia was defined as pneumonia which developed after 48 hours of hospitalization or within 14 days of previous hospitalization. Microbiological diagnosis methods included cultures of sputum, bronchoscopy with bronchoalveolar lavage (BAL) and/or protected brush specimens, pleural fluid, and blood. Pneumonia was microbiologically documented if cultures of sputum showed one or more potentially pathogen microorganism and microscopical examination showed more than 25 polymorphonuclear cells and fewer than ten epithelial cells per low-power (×100) field. A polimicrobial infection was diagnosed only if there was equally strong evidence for two or more pathogens. For each pathogen identified, susceptibilities to a standard panel of antibiotic agents were recorded [14].

Ventilator-associated pneumonia was not a focus of the study. Medical records were abstracted to determine the demographic, historical, and clinical information available to the admitting physicians at the time that a clinical diagnosis of nosocomial infection was made. These included date of birth, gender, race, known risk factors for HIV infection, and HIV disease stage at the time of evaluation. Data concerning the current episode of NBP were recorded, including clinical symptoms, roentgenographic picture, concurrent opportunistic diseases, white blood cell count (WBC), CD4+ count and arterial oxygen tension (PaO_2) at admission, bacterial isolation with antimicrobial susceptibility data, therapeutic regimens and follow-up data.

Analysis of Factors Influencing Prognosis

In considering age as a prognosis-influencing factor, we compared data between two groups – the first of patients 31 years old or younger, and the second of patients over 31 years of age.

Patients with a history of intravenous drug abuse were compared with patients who had other risk factors for HIV infection. The history of a previous AIDS diagnosis was defined according to the modified 1987 CDC criteria [14].

Patients diagnosed in the early phase of the study, prior to the availability of HAART for HIV disease (1988–1995) were compared with patients diagnosed in the last 7 years (1996–2002).

Early or late NBP was differentiated on the basis of onset time of respiratory symptoms: we defined early pneumonia the episode occurring during the first 4 days of hospitalization.

A diagnosis of respiratory failure was made when PaO_2 was less than 60 mmHg and/or arterial carbide oxide tension ($PaCO_2$) was equal to or higher than 50 mmHg while breathing room air.

Complicated pulmonary presentation was defined as the presence of pneumothorax, pleural effusions or multilobar involvement on thoracic roentgenograms.

Patients were differentiated in two groups according to their absolute neutrophil count/µl (ANC $<1{,}000$ or $\geq 1{,}000$) and according to CD4+ count/µl (<10 or ≥ 10 cells/µl) at the time of NBP diagnosis.

Three groups of etiologic pathogens were separately analyzed: (1) *Pseudomonas aeruginosa*, other *Pseudomonas* spp. (including *Stenotrophomonas maltophilia*), and gram-negative enteric bacilli (*Klebsiella* spp., *Escherichia coli* and others); (2) methicillin-resistant *Staphylococci* (MRSS); and (3) common agents of community-acquired pneumonia (CAP) (*Streptococcus pneumoniae*, other *Streptococci*, *Haemophilus influenzae*, and *Moraxella catarrhalis*).

Treatment regimens were evaluated using various criteria. First, we evaluated the effect of two types of treatment: (1) regimens including drugs against methicillin-resistant *Staphylococci* (MRSA), i.e., vancomycin and teicoplanin, and (2) regimens including drugs against *Pseudomonas aeruginosa* (i.e., ceftazidime, aminoglycosides, imipenem, piperacillin, and ciprofloxacin). Second, we compared treatments with a single antibiotic to those with antibiotic combinations. Third, we considered the adequacy of the antimicrobial regimen. The antibiotic treatment was considered "correct" if the empiric drug/s was/were in accord with the *in vitro* antibiotic susceptibility. In the absence of these conditions we considered the therapy to be "incorrect".

Deaths directly or indirectly related to NBP were combined into a single category, provided that they occurred before the episode of NBP was considered resolved.

Statistical Analysis

Quantitative variables were compared using ANOVA or Kruskal Wallis test. Differences between groups were assessed by the χ^2 test or Fisher exact test. Survival analysis and identification of prognostic factors for survival were done by univariate methods. Variables associated with mortality in the univariate analysis were entered in a multivariate regression analysis.

Results

Estimated Cumulative Incidence

During the 15-year study period, 4,967 patients known to be infected with HIV were admitted to our clinic. Among these, there were 120 episodes of microbiologically confirmed NBP in 107 HIV-infected inpatients. The estimated cumulative incidence of these NBP per year was 24 cases per 1,000 inpatients. The yearly incidence of NBP decreased over the study period, from 3.9 % in the pre-HAART era (1988–1995) to 0.8 % in the HAART era (1996–2002) ($p < 0.0001$).

Clinical and Radiological Features

Among the 105 HIV-infected inpatients with 120 episodes of NBP there were 78 males and 27 females. They ranged from 22 to 54 years (median 31 years); 78 % had a history of injection drug use, 12% of heterosexual intercourse and 10 % of homosexual intercourse. A total of 92 % of nosocomial pneumonia occurred in patients who had a previous diagnosis of AIDS. The mean time from AIDS diagnosis was 8.4 months (range 0–41 months, median 4). AIDS-related opportunistic diseases were common in our cohort. Those most frequently identified were tuberculosis (24%) and cytomegalovirus (CMV) infection (25%). In the majority of NBP a concurrent lung disease was detected (Table 1).

The median and mean absolute neutrophil counts (ANC) were 2,136 cells/µl and 2,835 cells/µl (range 400–12,160 cells/µl), respectively, and neutropenia $<1{,}000$ cells/µl was detected in 13 cases. The median and mean circulating CD4+ lymphocyte counts were 14 cells/µl and 38 cells/µl (range 0–548 cells/µl), respectively. 51 cases (41.5%) had <10 cells/µl, 54 (45%) had 10–99 cells/µl, 12 (10%) 100–199 cells/µl, and only three cases >200 cells/µl.

Several kinds of radiological presentation occurred. Many patients displayed new unilateral alveolar infiltrates

Table 1
Concurrent lung diseases in 120 episodes of nosocomial bacterial pneumonia.

	Number (%) of patients with indicated characteristic	
Neoplasia		
Kaposi's sarcoma	3/120	(2)
Lymphoma	2	(2)
Neoplasia and infection		
Kaposi's sarcoma + CMV	2	(2)
Kaposi's sarcoma + CMV + aspergillosis	2	(2)
Kaposi's sarcoma + PCP	1	(1)
Lymphoma + CMV	1	(1)
Infection		
Tuberculosis	26	(22)
PCP	18	(15)
CMV infection	4	(3)
Aspergillosis	3	(2)
MAC infection	1	(1)
MAC infection + PCP	1	(1)
MAC infection + aspergillosis	1	(1)
None	55	(46)

CMV cytomegalovirus infection; MAC *Mycobacterium avium* complex infection; PCP *Pneumocystis carinii (jirovecii)* pneumonia

(44.5%), but we also frequently observed diffuse interstitial infiltrates (24.2%), multiple alveolar infiltrates (13.3%), and mixed pictures. Pleural effusions were present in 12 patients (10%), in nine of these cases without presence of other opportunistic lung infections.

Microbiological Findings

Sites of bacterial isolation were BAL in 18 episodes, pleural fluid in four episodes, and sputum in the remaining cases. We described 11 episodes of early-onset and 109 of late-onset pneumonia. The most frequent pathogens isolated were *P. aeruginosa* (33%), *Staphylococcus aureus* (25%), *Streptococcus pneumoniae* (21%), and *Klebsiella pneumoniae* (12%) (Table 2). In 20 episodes (16.7%), two or more bacterial species were identified by culture. The same bacterial pathogens isolated from respiratory samples were also cultured from blood during 13 (10.8%) of 120 episodes. These included ten episodes of bacteremic *S. aureus*, and three episodes of pneumococcal bacteremia.

Some of the clinical features were compared on the basis of microbial etiologies (Table 3). We did not observe substantial differences in age, risk factor for HIV infection, WBC, LDH values, characteristics of radiographic pictures, or frequency of pulmonary comorbidity. Staphylococcal pneumonia was frequently characterized by the development of bacteremia (43% of the episodes) and higher mortality. Patients with pneumonia caused by methicillin-resistant *S. aureus* (MRSA), *P. aeruginosa* or enterobacteria tended to have CD4+ counts lower than patients with pneumonia due to CAP pathogens or methicillin susceptible *S. aureus* (MSSA) (27.43 ± 35.97 vs 67.28 ± 105.79 cells/µl, p = 0.007).

Antimicrobial Susceptibility Data

Since the three more frequent pathogens *(P. aeruginosa, S. aureus*, and *S. pneumoniae*) represented almost two-thirds of the isolates (94/146), data on *in vitro* susceptibility are primarily focused on these organisms. Data about *P. aeruginosa* were available for 38/39 isolates. The best results were obtained by tobramicin (3/38 resistant strains, 7.9%), imipenem (3/31, 9.7%), ciprofloxacin (4/34, 11.8%), ceftazidime, piperacillin and amikacin (5/38, 13.2%). Globally, 28/38 (73.7%) *P. aeruginosa* isolates were susceptible to all of the above mentioned drugs.

Data regarding antimicrobial susceptibility to *S. aureus* were available for all 31 cases. The only drugs showing low levels of resistance were vancomycin (0/31), chloramphenicol (1/31, 3.2%), and teicoplanin (1/23, 4.3%). Strains resistant to oxacillin were identified in 19/31 cases (61.3%). Similar rates of resistance were observed to rifampicin (58.1%), gentamicin (61.3%), and erythromycin (67.7%). Slightly better was the percentage of resistance to trimethoprim-sulphametoxazole (41.9%).

Data on antimicrobial susceptibility to *S. pneumoniae* was available in all 25 cases. None of the strains showed a decreased susceptibility to penicillin, whereas 24% of the isolates were resistant to erythromycin and 48% to trimethoprim-sulphametoxazole.

Among 31 gram-negative enterobacilli isolates, none showed resistance to imipenem or amikacin. All strains, except two *Acinetobacter calcoaceticus* isolates, were susceptible to ceftriaxone and aztreonam. The great majority of isolates was resistant to ampicillin (90.3%).

Antibiotic Therapy

In all but two patients, antibacterial therapy was begun prior to *in vitro* antimicrobial susceptibility results, and generally consisted of a single-drug therapy with an anti-pseudomonas drug. Drug combinations were started in a minority of cases (33/120, 27.5%). The antimicrobials most frequently adopted were fluoroquinolones (20.8%), ceftazidime (11.7%) or other cephalosporins (13.3%) and combinations of beta-lactam antibiotic plus beta-lactam inhibitor (13.3%). A glycopeptide antibiotic was part of initial treatment regimens in 8.3% of the cases. 27/120 (22.5%) cases of pneumonia did not receive correct antimicrobial therapy, based on current guidelines for treatment of NBP and on *in vitro* susceptibility data.

Table 2
Organisms cultured from the study participants with nosocomial bacterial pneumonia.

Organism	Early-onset Pneumonia (n = 11)	Late-onset Pneumonia (n = 109)	Total (n = 120)[a]	Mortality rate
Pseudomonas aeruginosa	4	35	39 (33%)	9 (23%)
Staphylococcus aureus	2	29	31 (26%)	
MSSA	2	10		2 (17%)
MRSA	–	19		11 (58%)
Streptococcus pneumoniae	3	22	25 (21%)	3 (12%)
Klebsiella pneumoniae	1	13	14 (12%)	3 (21%)
Haemophilus influenzae	–	8	8 (7%)	1 (12%)
Pseudomonas, others	1	5	6 (5%)	1 (17%)
Enterobacter spp.	1	3	4 (3%)	–
Klebsiella, others	–	4	4 (3%)	1 (25%)
Escherichia coli	–	3	3 (3%)	1 (33%)
Streptococcus, others	1	2	3 (3%)	–
Staphylococcus haemolyticus	–	2	2 (2%)	1 (50%)
Moraxella catarrhalis	1	1	2 (2%)	–
Citrobacter spp.	–	2	2 (2%)	–
Acinetobacter spp.	–	2	2 (2%)	–
Serratia marcescens	–	1	1 (1%)	–
Proteus mirabilis	–	1	1 (1%)	–

MSSA methicillin susceptible *Staphylococcus aureus*; MRSA methicillin resistant *Staphylococcus aureus*; [a] Twenty nosocomial lung infections were polimicrobial

Mortality Rate and Outcome-Associated Factors

Univariate Analysis

The mortality rate for HIV-infected patients who developed NBP was 25.8% (31/120). The outcome of NBP varied according to etiology. In fact, the mortality rate reached 57% when methicillin-resistant staphylococci were identified among the etiologic agent/s of the pneumonia (OR 5.61, $p < 0.001$). On the contrary, the mortality rate decreased to 11% when *S. pneumoniae, H. influenzae,* or *M. catarrhalis* were the unique etiologic agents of pneumonia (OR 0.29, $p = 0.05$).

Although the etiology of pneumonia was the only factor significantly associated with increased risk of adverse outcome, univariate analysis showed that other factors, although not of statistical significance, might be associated with shorter survival. In particular, survival seemed to be shorter among patients with an absolute CD4+ count <10 cells/µl (OR 2.35, $p = 0.06$), a concomitant lung neoplasm (OR 2.66, $p = 0.15$) or a complicated roentgenographic picture at the onset (OR 2.33, $p = 0.08$), and among those patients

Table 3
Selected characteristics of monomicrobial nosocomial pneumonia on the basis of microbial etiology.

	A) Pseudomonas *spp.* (n = 35)	B) Enterobacteria (n = 15)	C1) MRSS (n = 17)	C2) MSSA (n = 6)	D) CAP bacteria (n = 26)	Statistical significance
Age, years (mean)	32	34	38	32	32	Ns
CD4 count/µl (mean)	26	26	31	71	64	A vs D <0.05 A vs C2 <0.05
WBC/µl (mean)	3,587	3,390	4,180	4,727	4,095	Ns
LDH IU/l (mean)	858	699	693	673	503	Ns
Intravenous drug abuse as risk factor	24 (69%)	12 (80%)	15 (82%)	4 (67%)	18 (69%)	Ns
Complicated X-rays picture	10 (29%)	2 (13%)	7 (41%)	3 (50%)	4 (15%)	Ns
Bacteremic episodes	0	0	7 (41%)	3 (50%)	3 (12%)	A/B vs C p <0.001 D vs C p <0.05
Pulmonary comorbidity	20 (57%)	9 (60%)	10 (59%)	3 (50%)	14 (54%)	Ns
Overall mortality	8 (23%)	6 (40%)	10 (59%)	2 (33%)	2 (8%)	D vs C/B p <0.005 A vs C p <0.05

MRSS methicillin resistant *Staphylococcus species* (15 *S. aureus* and 2 *S. haemolyticus*); MSSA methicillin susceptible *Staphylococcus aureus*; CAP bacteria community-acquired pneumonia (*S. pneumoniae*, *H. influenzae, M. catarrhalis, Streptococci,* others)

Table 4
Univariate analysis of factors associated with fatality of 120 nosocomial bacterial pneumonia in HIV-infected patients.

Factors	Death/total (%)	Crude OR	χ^2 test p-value
Sex			
Female	7/30 (23)	1	
Male	24/90 (27)	1.20	0.81
Age			
< 31	11/53 (21)	1	
≥ 31	20/67 (30)	1.62	0.30
Intravenous drug use			
No	5/26 (19)	1	
Yes	26/94 (28)	1.61	0.46
AIDS diagnosis			
No	3/10 (30)	1	
Yes	28/110 (26)	0.80	0.72
Comorbidity			
No	4/15 (27)	1	
Yes	27/105 (26)	0.95	1.00
Date of onset			
HAART era (96–2002)	4/17 (24)	1	
Pre-HAART era (88–95)	27/103 (26)	1.16	1.00
Pneumonia onset			
Early	2/11 (18)	1	
Late	29/109 (27)	1.63	0.77
Absolute neutrophil count			
< 1,000/μl	3/13 (23)	1	
≥ 1,000/μl	28/107 (26)	1.18	1.00
CD4+ cells count			
≥ 10/μl	13/69 (19)	1	
< 10/μl	18/51 (35)	2.35	0.06
PaO_2			
< 60 mmHg	3/16 (19)	1	
≥ 60 mmHg	28/104 (27)	0.63	0.76
Roentgenographic picture			
Not complicated	20/92 (22)	1	
Complicated	11/28 (39)	2.33	0.08
Concomitant lung neoplasia			
No	26/109 (24)	1	
Yes	5/11 (46)	2.66	0.15
Concomitant lung infection			
Yes	13/54 (24)	1	
No	18/66 (27)	0.85	0.83
Bacteremic pneumonia			
No	26/107 (24)	1	
Yes	5/13 (39)	1.95	0.32

Continued next page

treated with an incorrect antimicrobial regimen (OR 2.01, p = 0.14) or with glycopeptide antibiotics (OR 3.23, p = 0.12) (Table 4).

Age, gender, risk factor for HIV, previous AIDS diagnosis, ANC, comorbidity, date of the NBP episode, pneumonia onset (early or late), concomitant lung infections, and PaO_2 levels were not significantly associated with increased risk of adverse outcome in the univariate analysis.

Multivariate Analysis

For the multivariate analysis, we considered the two statistically significant factors in univariate analysis (CAP pathogens or MRSS as etiological agent of pneumonia) and other statistically insignificant factors likely to influence mortality (CD4+ count < 10 cells/μl, presence of concomitant lung neoplasm, characteristic of the roentgenographic picture, use of glycopeptide as initial antibiotic treatment and correctness of antimicrobial treatment). When all these factors were included in a multivariate model, only one factor remained significantly associated with lower survival: a methicillin-resistant *Staphylococcus* acting as an etiologic agent of pneumonia (RR 4.05; 95% confidence interval, 1.076–15.239; p < 0.05) (Table 5).

Discussion

To our knowledge, the results described above are taken from the largest population-based study to date to report the microbiological and clinical characteristics of NBP in persons with HIV infection. Because we did not include cases without microbial diagnosis, our figures underestimate the actual incidence of NBP. Previous cohort studies performed between 1989 and 1996 reported overall incidence rates of 12–33 NBP episodes per 1,000 admissions [8, 9, 15]. At 25 cases per 1,000 hospital admissions, our results fall in this same range. In reality, this rate showed large variations between the pre-HAART era (39 per 1,000 admissions) and the post-HAART era (8 per 1,000 admissions), as has been described by other researchers [11]. The decline of NBP was expected, due to the ameliorated condition of AIDS patients

Table 4 (**Continued**)

Factors	Death/total (%)	Crude OR	χ^2 test p-value
Etiology (I)			
Other bacteria	16/57 (28)	1	
Gram negative enteric bacilli and *Pseudomonas* spp.	15/63 (24)	0.80	0.68
Etiology (II)			
Other bacteria	19/99 (19)	1	
MRSS	12/21 (57)	5.61	0.001
Etiology (III)			
Other bacteria	28/93 (31)	1	
CAP pathogens only	3/27 (11)	0.29	0.05
Therapy (I)			
Correct	21/93 (23)	1	
Uncorrect	10/27 (37)	2.02	0.14
Therapy (II)			
Antibiotic combination	7/33 (21)	1	
Monotherapy	24/87 (28)	1.41	0.64
Therapy (III)			
Other therapy	15/53 (28)	1	
therapy against *Pseudomonas*	16/67 (24)	0.79	0.68
Therapy (IV)			
Other therapy	26/110 (24)	1	
therapy against MRSS	5/10 (50)	3.23	0.12

OR odds ratio; HAART highly active antiretroviral therapy; MRSS methicillin-resistant *Staphylococcus* spp; CAP (community acquired pneumonia) pathogens including *S. pneumoniae* and other *Streptococci*, *H. influenzae* and *M. catarrhalis*

Table 5
Multivariate analysis of outcome-associated factors: predictors of survival in 120 episodes of nosocomial bacterial pneumonia in HIV-infected patients. Analysis performed by multivariate logistic regression analysis.

Negative predictors (associated with reduced survival)	Relative Risk (95% CI)	p-value
Incorrect antibiotic therapy	1.43 (0.433–4.717)	0.558
Glycopeptide treatment at the onset	1.66 (0.303–9.067)	0.560
Etiologic agents other than CAP pathogens[a]	1.89 (0.132–2.122)	0.370
Complicated lung presentation	1.92 (0.555–9.775)	0.213
Presence of concomitant neoplastic lung disease	2.33 (0.688–5.367)	0.248
CD4+ count < 10/µl	2.39 (0.916–6.232)	0.075
Methicillin-resistant staphylococcal pneumonia	4.05 (1.076–15.239)	0.039

A p value of < 0.05 was considered statistically significant. [a] CAP (community-acquired pneumonia) pathogens included *S. pneumoniae* and other streptococci, *H. influenzae* and *M. catarrhalis*

and shorter hospitalization stays which have been a result of treatments with HAART.

In the general population, *P. aeruginosa* is the most frequently isolated pathogen for NBP, followed by *S. aureus* and various members of the *Enterobacteriaceae* family [16]. In AIDS patients, NBP has been deemed to be caused by these same pathogens [17, 18]. The best characterized study on this matter confirmed the prevalence of *P. aeruginosa*, followed by *S. aureus* [11]. Autopsy studies further corroborate the importance of these two agents [12].

Our endeavor to identify selected characteristics of NBP on the basis of microbial etiology has been unsuccessful. Etiologic cause of pneumonia is not predictable on the basis of WBC and CD4+ count, roentgenographic picture, risk factors for HIV infection, or pulmonary comorbidity. The only significant feature was that, compared to *P. aeruginosa* and MRSA, agents commonly observed in CAP (including MSSA) caused pneumonia in patients with higher CD4+ counts.

Data on antimicrobial resistance produced a picture which contrasts with those usually observed in intensive care units. In particular, multiresistance of *Pseudomonas* was very rare and almost three-quarters of the isolates were susceptible to ceftazidime, ciprofloxacin, aminoglycosides, imipenem, and ureidopenicillins. Another study in Spain produced exceedingly similar data [19].

Our data on *S. aureus* susceptibility reflects the reality of the Italian situation, where MRSA have >40% frequency in the largest teaching hospital [20]. About two-thirds of the isolates were resistant to oxacillin, erythromycin and gentamicin. Resistance of *S. pneumoniae* to penicillin is increasing worldwide among HIV-infected patients as well [21, 22]. In our series, we did not register cases of penicillin-resistant *S. pneumoniae* infection, whereas episodes caused by macrolide-resistant strains were increasing.

The overall mortality rate of nosocomial pneumonia in the general population is 20–50% [23]. In two series of HIV-infected patients, nosocomial

pneumonia was associated with fatality rates varying from 29% to 80% [24, 25]. In our patients the mortality rate was approximately 26%, but the study did not include patients with advanced AIDS, from whom collection of valuable sputum specimens was impossible, as invasive procedures to establish the diagnosis of NBP were often unfeasible.

Several studies focusing on the outcome of nosocomial pneumonia have identified factors influencing mortality in affected patients. The principal factors worsening the prognosis were age over 60 years, underlying condition of the host, development of respiratory failure, bilateral involvement of the lungs, acquisition of pneumonia in ICU settings, identification of "high risk" microorganisms (especially *P. aeruginosa*, but also other gram-negative bacilli, enterococci and *S. aureus*), and inappropriate antibiotic therapy [26]. Among HIV-infected patients, factors associated with bacterial-related mortality also included low number of CD4+ or polymorphonuclear cells, low PaO_2 gas level and low Karnofsky scores [25]. We analyzed several of the above mentioned factors, and multivariate analysis revealed that only one variable reached statistical significance: methicillin-resistant staphylococci as causative agents of lung infection. However, other factors correlate with reduced survival: low CD4+ cell count (<10 cells/µl), complicated roentgenographic presentation, concomitant lung neoplasm, and inappropriate antimicrobial treatment. Moreover, our study confirms the substantial difference between low and high risk pathogens, including pneumococci and *H. influenzae* in the former group, whereas in the latter *S. aureus* plays the primary role in influencing mortality with respect to gram negative bacteria. This is in apparent contrast with the common opinion that *P. aeruginosa* is the pathogen more frequently associated with excess mortality of NBP [25, 27, 28]. A number of possible explanations for our results are conceivable. First, in choosing empirical antibiotic treatments, much attention was given to *P. aeruginosa* pneumonia, when in fact, in initial antibiotic treatment, antipseudomonal agents were adopted six times more frequently than antibiotics against MRSA. Second, we cannot exclude the possibility of higher frequency of *P. aeruginosa* pneumonia in patients with advanced AIDS disease in which it was impossible to obtain significant biological samples. Third, it is reasonable to argue that only studies performed in populations with very high frequencies of MRSA would be able to highlight the influence of methicillin resistance on the outcome of NBP.

Data collected on antimicrobial susceptibility provide more information about the optimization of antimicrobial treatment on empirical basis. Imipenem was the antibiotic with the best *in vitro* spectrum of activity against gram-negative pathogens, but ciprofloxacin, ceftazidime, piperacillin, the aminoglycosides and, to lesser degree, aztreonam, were useful alternatives, albeit in settings of multiple drug treatment. Aminopenicillins (±beta-lactamase inhibitors) or ceftriaxone would be inappropriate if given in a nonselective fashion.

The results of this study do not support the use of glycopeptides as initial empiric therapy, because the few patients initially treated with these drugs did not show an improved prognosis. However, MRSA is a frequent cause of NBP in patients with very advanced HIV disease and the only significant predictive factor for an adverse outcome in our series. Therefore, it may be appropriate, only in patients with worse prognosis, to consider empiric vancomycin/teicoplanin therapy, while awaiting the results of sputum cultures or invasive procedures. Among these subjects we would include, on the basis of prognostic factors, those with very low CD4+ counts, complicated X-rays or coexisting lung cancer, in addition to those at risk of MRSA infection.

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