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Study objectives: **To assess the outcome and the prognostic factors in 200 non-HIV immunocompromised patients with pulmonary infiltrates (PIs).**
Design: **Prospective observational study.**
Setting: **An 800-bed university hospital.**
Patients: **Two hundred non-HIV immunocompromised patients (hematologic malignancies, 79 patients; hematopoietic stem cell transplants [HSCTs], 61 patients; and solid-organ transplants, 60 patients).**
Methods: **Investigation of prognostic factors related to mortality using a multiple logistic regression model.**
Results: **Specific diagnosis of the PI was obtained in 78% of the cases (infectious origin was determined in 74%). The overall mortality rate was 39% (78 of 200 patients). Patients with HSCT had the highest mortality rate (53%). A requirement for mechanical ventilation (odds ratio [OR], 28; 95% confidence interval [CI], 9 to 93), an APACHE (acute physiology and chronic health evaluation) II score of > 20 (OR, 5.5; 95% CI, 2 to 14.7), and a delay of > 5 days in establishing a specific diagnosis (OR, 3.4; 95% CI, 1.2 to 9.6) were the variables associated with mortality at the multivariate analysis. The subgroup analysis based on underlying disease confirmed the prognostic significance of these variables and the infectious etiology for the PI.**
Conclusions: **Mortality in immunocompromised patients is high, particularly in patients undergoing HSCT. Achieving an earlier diagnosis potentially may improve the mortality rate of these patients.** ***(CHEST 2002; 122:253–261)***

Key words: immunosuppression; lung infection; mechanical ventilation; prognosis

Abbreviations: APACHE = acute physiology and chronic health evaluation; CI = confidence interval; HM = hematologic malignancy; HSCT = hematopoietic stem cell transplant; MV = mechanical ventilation; OR = odds ratio; PI = pulmonary infiltrate; SOT = solid organ transplant

Immunocompromised patients are at high risk for developing infectious and noninfectious pulmonary complications.[1–4] The mortality rate associated with pulmonary complications is exceedingly high, reaching 85% in some series.[5] Some reports have suggested that the prognosis of these patients might be improving, especially within certain groups of immunocompromised patients.[6] New molecular diagnostic techniques, more effective prophylactic treatments, and reduced toxicity of conditioning regimens likely might be contributing to this improvement in prognosis.[7,8] There is also general agreement that the severity of pulmonary involvement (reflected by the presence of acute respiratory failure and, specifically, by the need for mechanical ventilation [MV]) is an ominous prognostic factor in hematopoietic stem cell transplant (HSCT) recipients. In this group of immunocompromised patients,

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the mortality rate for those requiring MV is > 90%, and very few survive 6 months after the onset of the pulmonary complication.[9] The impact of respiratory failure and the need for MV in other groups of immunocompromised patients has not been well-elucidated. More controversial is the significance of certain other factors as follows: identification of a specific etiologic diagnosis; the role of bronchoscopy[10]; or the inadequacy of empirical treatment in the final outcome.[11,12] This information may be decisive from a clinical point of view and for designing cost-effective diagnostic strategies. In a study involving patients with different types of immunosuppression, Poe et al[1] concluded that obtaining a specific diagnosis with the use of pulmonary biopsy did not influence outcome. Surprisingly, in the series of Poe et al,[1] patients with an etiologic diagnosis who had undergone specific treatment of the pulmonary complication seemed to have a worse prognosis than those without. By contrast, more recent studies suggest that an aggressive approach in immunocompromised patients may improve their outcomes.[13,14] Finally, it is not clear which factors are relevant for different specific groups of immunocompromised patients and which can be applied to the population in its entirety.

Recently, we have reported[7] on the clinical characteristics and diagnostic yield of different noninvasive and bronchoscopic techniques in a population of non-HIV immunocompromised patients with pulmonary infiltrates (PIs). Based mainly on this population, the present study assesses prognostic factors that are related to mortality. Specifically, we were interested in knowing whether some of the prognostic factors influencing outcome in a particular group of immunocompromised patients also could be applied to other immunocompromised groups and which of these factors might be amenable to medical intervention.

Materials and Methods

Patients

Two hundred consecutive non-HIV immunocompromised patients with a first episode of PIs were evaluated prospectively from February 1998 to January 2001. The patient group was composed of 60 patients who had received solid organ transplants (SOTs; renal, 24 patients; liver, 19 patients; cardiac, 11 patients; and renopancreatic, 6 patients), 61 HSCT recipients, and 79 patients with hematologic malignancies (HMs) treated with chemotherapy. The underlying HMs of the 140 patients in the HSCT and HM groups were acute myeloid leukemia (35 patients; 25%), Hodgkins lymphoma (18 patients; 13%), acute lymphoid leukemia (16 patients; 12%), chronic lymphoid leukemia (14 patients; 10%), multiple myeloma (13 patients; 9%), non-Hodgkins lymphoma (10 patients; 7%), and others (34 patients; 24%).

Diagnostic Procedures

Within the first 24 to 48 h after the identification of the PI, samples of blood were drawn for culture and antigen testing (*ie*, pp65 cytomegalovirus and Aspergillus spp galactomannan antigen). A sample of spontaneous or induced sputum was obtained. A Gram stain was performed to assess the quality of the sputum.[15] A sample of nasopharyngeal wash was taken for viral detection and tissue culture. Bronchoscopic methods included protected-specimen brush, bronchial aspirate, and BAL. Although the primary intention was to perform all the above-referred diagnostic procedures in all patients, the ultimate decision as to which of the procedures should be performed was always determined by the clinical state of the patient and the criteria of the physician in charge. Other diagnostic techniques such as transbronchial biopsy and open lung biopsy were carried out in selected patients.

The Ethics Committee of the Hospital Clínic approved the study protocol. Informed consent was obtained from the patients who had been referred for a bronchoscopic exploration. The details of the laboratory procedures and the diagnostic criteria for the etiology of PI have been described in a previous article.[7]

Recorded Variables

The following categoric variables were recorded: age; sex; underlying disease; prophylactic antibiotic treatment within the last month; previous admission to hospital within the last month; time between the onset of symptoms and appearance of radiographic infiltrates (> 7 days/< 7 days); presence of neutropenia; presence of graft-vs-host disease; admission to the ICU; specific etiology of the PI (infectious vs noninfectious); community vs nosocomial pneumonia; pattern of radiographic infiltrates (focal vs diffuse); inadequate empirical treatment; and requirement for MV. The continuous variables that were recorded were as follows: leukocyte and platelet counts; prothrombin rate; creatinine, serum albumin, and protein levels; Pao_2/fraction of inspired oxygen ratio; and acute physiology and chronic health evaluation (APACHE) II score.[16]

Definition

Etiology of the PI: The PI was considered to be infectious when there was clinical suspicion of a lower respiratory tract infection and a microbial agent was isolated in respiratory and/or nonrespiratory samples. Pulmonary infection was considered to be nosocomial (in-hospital) on appearance after 72 h of hospital admission. Noninfectious PIs were considered when the clinical data did not suggest an infectious etiology, no microbiological agents were isolated in any processed sample, and the clinical course and response to treatment were in accordance with an alternative noninfectious etiology.

Prophylactic Antibiotic Treatment: This was defined as the administration of prophylactic antibiotics during the last month previous to the onset of PIs.

Inadequate Empirical Treatment: This was defined as empirical treatment that was administered that does not specifically cover the particular etiology of the PI (both infectious or not infectious).

Diagnosis Delay: This was defined as the period of time between the day the presence of PIs was first demonstrated and the day that results of the diagnostic procedure were available.

Mortality: This was defined as in-hospital death.

Statistical Analysis

Differences between groups of immunocompromised patients and between survivors and nonsurvivors were assessed using the

Mann-Whitney *U* test for continuous variables, the χ^2 test for categoric variables, and the Fisher exact test in the case of small expected frequencies. The variables analyzed were those selected as potential predictors of outcome in this population according to the literature.[1,8,15,17–19] Some continuous variables were categorized. In order to optimize the threshold that would discriminate between survivors and nonsurvivors, the formula for threshold computation based on the median value (*ie*, the 50th percentile) was used. The influence of several variables on mortality was evaluated by univariate analysis using the χ^2 test (or the Fisher exact test). Thereafter, a multiple logistic regression model was applied to the variables found to be significantly associated with death. Multiple logistic regression analysis permitted an estimate of the odds ratio (OR) of death and a calculation of the 95% confidence interval (CI). A multivariate analysis of prognostic factors was performed for the whole population (n = 200) and for the following three different groups of patients studied: HSCT, 61 patients; HM, 79 patients; SOT, 60 patients. All statistics were calculated using a statistical software package (SPSS for Windows, version 10.0; SPSS; Chicago, IL). All p values reported are two-tailed, and the data are presented as the mean ± SD or as a percentage.

Results

Clinical Characteristics and Etiology of PIs

Of the 200 immunocompromised patients included in the present study, 109 (54%) were admitted to the ICU and 92 (46%) required MV. The clinical characteristics of the three groups of patients evaluated were similar (Table 1), except for gender (*ie*, more men among the SOT patients), neutropenia (*ie*, fewer cases among the SOT patients), and prophylactic antibiotic treatment (*ie*, more frequent among HSCT patients). Patients with HMs did not require MV as often as those in the other two groups. Patients who had received HSCTs had lower hematocrits and platelet counts. Creatinine levels were higher in SOT patients. Overall, a definite etiology was established in 157 cases (78%). Of the 157 patients with specific diagnoses, this information was obtained using noninvasive techniques in 44% and bronchoscopic techniques in 56%. The etiology of the PIs was infectious in 116 of 157 patients (74%), and it was noninfectious in 41 of 157 patients (26%). The different etiologies of PI are reported in Table 2. Of the infectious etiologies, bacteria were the most common microorganisms causing PI (46 of 116 patients; 23%), followed by fungi (30 patients; 15%), virus (20 patients; 10%), mixed infections (15 patients; 8%), and other infectious etiologies (5 patients; 2%). All infectious agents are summarized in Table 3. Table 4 shows the diagnostic yield of the different noninvasive and bronchoscopic techniques.

Table 1—*Clinical Characteristics of the Different Immunocompromised Groups Evaluated (n = 200)**

Variables	HSCT (n = 61)	HMs (n = 79)	SOT (n = 60)	p Value
Categoric				
Gender				
Male	38	44	47	0.02
Female	23	35	13	
Prophylactic antibiotic treatment	53 (87)	45 (57)	27 (45)	0.0001
Prior admission to hospital	19 (31)	22 (28)	12 (20)	0.36
APACHE II score > 20	25 (41)	30 (38)	23 (38)	0.93
Delay in diagnosis > 5 d	15 (34)	29 (55)	22 (58)	0.06
Acute onset of PI	36 (72)	44 (76)	49 (89)	0.07
Bilateral infiltrates in chest radiograph	37 (61)	41 (28)	28 (47)	0.3
Pao_2/Fio_2 < 250 mm Hg	37 (61)	41 (28)	28 (47)	0.3
Neutropenia†	26 (43)	34 (43)	3 (5)	< 0.0001
Infectious etiology	33 (70)	43 (75)	40 (75)	0.8
Nosocomial pneumonia	27 (63)	28 (46)	27 (66)	0.3
MV	30 (49)	25 (32)	37 (62)	0.002
Inadequate empirical treatment	26 (55)	22 (38)	18 (34)	0.08
Undiagnosed	14 (23)	22 (28)	7 (12)	0.07
Mortality	32 (53)	23 (29)	23 (38)	0.02
Continuous				
Age, yr	41 ± 12	52 ± 18	52 ± 14	< 0.0001
APACHE II score	18 ± 7	18 ± 7	20 ± 8	0.6
Hospital stay, d	29 ± 19	29 ± 17	26 ± 24	0.7
ICU stay, d	11 ± 9	13 ± 12	17 ± 14	0.08
MV, d	9 ± 9	11 ± 10	14 ± 13	0.22
Hematocrit, %	27 ± 5	29 ± 6	30 ± 4	0.014
Platelets, 10^9 cells/L	53 ± 56	94 ± 100	110 ± 81	0.001
Creatinine, mg/L	1.6 ± 1.4	1.1 ± 0.7	3.2 ± 2.3	< 0.0001
Albumin, g/L	30 ± 5	31.7 ± 5	31.8 ± 6	0.6

*Values given as No. (%) or mean ± SD, unless otherwise indicated. Fio_2 = fraction of inspired oxygen.
†Neutropenia was defined as a granulocyte count of < 1,000 cells/μL.

Table 2—*Etiologic Diagnosis in Relation to the Underlying Immunosuppressed Condition

Variables	HSCT (n = 61)	HMs (n = 79)	SOT (n = 60)	Total (n = 200)	p Value
Bacterial	7 (11)	18 (23)	21 (35)	46 (23)	0.009
Fungal	8 (13)	15 (19)	7 (12)	30 (15)	0.4
Viral	12 (20)	6 (8)	2 (3)	20 (10)	0.007
Polymicrobial	5 (8)	1 (1)	9 (15)	15 (7.5)	0.009
Other infectious etiologies†	1 (2)	3 (4)	1 (2)	5 (2.5)	0.6
Pulmonary edema	3 (5)	3 (4)	11 (18)	17 (8.5)	0.005
DAH	5 (8)	3 (4)	2 (3)	10 (5)	0.4
BOOP	2 (3)	3 (4)		5 (2.5)	0.3
Other noninfectious etiologies‡	4 (7)	5 (6)		9 (4.5)	0.13
Undetermined	14 (23)	22 (28)	7 (12)	43 (22)	0.07

*Values given as No. (%), unless otherwise indicated. DAH = diffuse alveolar hemorrhage; BOOP = bronchiolitis obliterans organizing pneumonia.

†Includes tuberculosis (three patients) and *Pneumocystis cannii* pneumonia (two patients).

‡Includes five cases of pulmonary involvement of Hodgkins disease, two cases of drug toxicity due to bleomycin, one case of alveolar proteinosis, and one case of sarcoidosis.

Mortality Rate

The crude mortality rate was 39% (78 of 200 patients). The mortality rate among patients with infectious PIs was 51% (59 of 116 patients), and the mortality rate among patients with noninfectious PIs was 17% (7 of 41 patients) [$p < 0.0001$]. No differences were observed in mortality rates between the different infectious etiologies (*ie*, bacterial, fungal, and viral). The mortality rate in undiagnosed patients was 28% and in patients with a specific diagnosis, 42% ($p = 0.1$). The mortality rate was higher in patients who had received HSCTs (53%) than in those who had received SOTs (38%) or those who had HMs (29%) [$p = 0.02$; Table 1].

Prognostic Factors

Univariate Analysis for the Whole Population: Ten variables were associated with increased mortality rate in the univariate analysis of the whole population (Table 5). Variables reflecting the severity of the disease, such as an APACHE II score of > 20 and the presence of bilateral infiltrates on chest radiographs, had a decisive influence on mortality rate. The requirement for MV had the strongest association with mortality rate. Hypoalbuminemia, an acute onset of PIs, the infectious etiology of the PI, and a nosocomial origin of infection also were associated with a higher mortality rate. Finally, three variables that are amenable to potential medical intervention, such as prophylactic antibiotic treatment, inadequacy of empirical treatment, and delay of more than 5 days (the median value for the delay in establishing the diagnosis of the whole population) in establishing the diagnosis were associated with poor outcomes.

Multivariate Analysis for the Whole Population: We used a multivariate statistical approach to identify which significant factors in the univariate analysis were independently related to mortality rate. A requirement for MV, an APACHE II score of > 20, and a delay in diagnosis of > 5 days were the variables selected in the model when the whole population was analyzed. The simultaneous presence of these three factors was associated with a mortality rate of 92% (31 of 34 patients; OR, 32; 95% CI, 9.5 to 112), whereas their absence was associated with a mortality rate of only 3% (1 of 34 patients; $p < 0.0001$). The mortality rate in intubated patients was 77% (71 of 92 patients; OR, 49; 95% CI, 20 to 121), and in nonventilated patients it was 6% (7 of 108 patients; $p < 0.0001$). The median APACHE II score in the 200 patients evaluated was 18 (range, 5 to 40). The median APACHE II score among the survivors was 14 ± 5, and it was 25 ± 6 among nonsurvivors ($p < 0.0001$). There was no difference among the three types of immunocompromised patients evaluated regarding the APACHE II score. No patient with an APACHE II score of ≥ 26 at hospital admission survived to hospital discharge. The mortality rate among patients in whom the diagnosis was established during the first 5 days was 32% (24 of 74 patients), and among patients in whom the diagnosis was established later it was 51% (42 of 83 patients; $p = 0.024$). The delay in diagnosis was also a variable related to mortality rate when only patients with an infectious etiology (n = 116) of the PI were evaluated. Thus, the mortality rate in this subgroup of immunocompromised patients was 38% (18 of 47 patients) when the diagnosis was established during the first 5 days and 60% (41/69 patients) when the diagnosis was established later ($p < 0.03$).

Different Groups of Immunocompromised Patients: Table 6 shows the variables related to mortality rate for the different groups of immunocompro-

Table 3—*Infectious Pathogens Isolated in 116 Patients (74%) With an Infectious Etiology of the PI

Pathogens	Cases, No.
Bacterial	
Gram-positive	
S aureus†	13
Streptococcus pneumoniae	3
Streptococcus mitis	1
Nocardia asteroides	1
Gram-negative	
Escherichia coli	7
Pseudomonas aeruginosa	6
Acinetobacter baumanii	3
Serratia marcescens	2
Klebsiella pneumoniae	1
Morganella morganii	1
Stenotrophomones maltophilia	1
Proteus mirabilis	1
Other bacteria	
Legionella pneumophila	3
Chlamydia pneumoniae	2
Mycoplasma pneumoniae	1
Fungal	
Aspergillus fumigatus	20
Candida albicans	6
Candida kruseii	1
Candida tropicalis	1
Scedosporium prolificans	1
Penicillium purpurogenum	1
Viral	
CMV	8
Influenza A virus	4
Respiratory syncytial virus	4
Parainfluenzae virus type 3	2
VHS-1	2
Others	
Mycobacterium tuberculosis	3
Pneumocystis carinii	2
Mixed infections	
Aspergillus sp + MRSA	3
Aspergillus sp + *P aeruginosa*	1
E coli + *K pneumoniae* + *S maltophilia* + *P aeruginosa*	1
Aspergillus sp + CMV	1
Citrobacter freundii + *P aeruginosa*	1
MRSA + *Enterococcus fecalis*	1
A fumigatus + VHS-1	1
A baumanii + *P aeruginosa*	1
Aspergillus flavus + *Enterococcus faecium* + CMV	1
A fumigatus + *S pneumoniae*	1
Aspergillus niger + *E coli* + MRSA	1
P aeruginosa + CMV	1
C tropicalis + *A fumigatus* + *P aeruginosa*	1

*MRSA = methicillin-resistant *S aureus*; CMV = cytomegalovirus; VHS = virus herpes simplex.
†Nine cases were MRSA.

Table 4—*Diagnostic Yield of the Different Procedures Performed

Diagnostic Techniques	Positive/Performed
Blood cultures	32/192 (17)
Aspergillus antigen detection	12/66 (18)
CMV antigen detection	14/98 (14)
Nasopharyngeal wash	13/60 (22)
Sputum	20/78 (26)
Bronchial aspirate	47/89 (53)
Protected specimen brush	31/129 (24)
Bronchoalveolar lavage	70/140 (50)
Transbronchial biopsy†	6/12 (50)
Open lung biopsy‡	2/2 (100)

*Values given as No./Total No. (%). See legends of Tables 2 and 3 for abbreviations not used in the text.
†Includes two cases of BOOP, two cases of pulmonary involvement of Hodgkins disease, and two cases of bacterial pneumonia.
‡Includes one case of pulmonary tuberculosis and one case of BOOP.

mised patients. Interestingly, two variables related to mortality rate when the whole population was studied (*ie*, the need for MV and an APACHE II score > 20) also had prognostic significance in each of the three different subgroups. Similarly, an infectious etiology for the PI was a variable with prognostic significance for each of the different groups. Table 7 shows the variables with prognostic significance in each group of immunocompromised patients when evaluated on a multivariate basis. The need for MV was the only variable that significantly affected mortality rate in HSCT patients. APACHE II score and an infectious etiology of the PI also had prognostic significance in patients with HMs. Finally, APACHE II score and diagnosis delay were the dominant independent variables that significantly predicted mortality in SOT patients.

Discussion

The results of the present study show that a high APACHE II score at diagnosis, the need for MV, and a delay in establishing a specific diagnosis are factors associated with mortality rate in a mixed population of immunocompromised patients. The analysis of each type of immunosuppression confirmed the prognostic relevance of the above-mentioned variables and also the significance of an infectious etiology for the infiltrates.

The in-hospital mortality rate of our population of immunocompromised patients as a whole was 39% (78 of 200 patients). The mortality rate among HSCT patients was almost twofold higher than that of patients with HMs or of those who had received SOTs. Although other studies have confirmed the high mortality rate in patients who had received HSCTs and those with HMs with pulmonary complications,[20,21] there is little information in the literature regarding the mortality rate in patients who had received SOTs and those with PIs. Torres et al[22] found a 32% mortality rate in a series of 50 patients

Table 5—*Comparison Between Survivors and Nonsurvivors for All Groups of Immunocompromised Patients Evaluated

Variables	All Patients (n = 200)	Survivors (n = 122)	Nonsurvivors (n = 78)	p Value†	OR (95% CI) [p Value]‡
Gender					
Male	129	82	47	0.4	
Female	71	40	31		
Prophylactic antibiotic treatment	125 (63)	66 (54)	59 (76)	0.003	
Prior admission to hospital	53 (27)	28 (23)	25 (32)	0.19	
APACHE II score > 20	78 (39)	17 (14)	61 (78)	< 0.0001	5.5 (2–14.7) [0.0007]
Delay in diagnosis > 5 d	83 (53)	41 (45)	42 (64)	0.024	3.4 (1.2–9.6) [0.018]
Acute onset of PI	129 (79)	69 (72)	60 (90)	0.006	
Bilateral infiltrates in chest radiography	106 (53)	56 (46)	50 (64)	0.014	
Albumin < 29 g/L	89 (51)	47 (42)	42 (69)	0.001	
Neutropenia	63 (31)	34 (28)	29 (37)	0.21	
Infectious etiology	116 (74)	57 (63)	60 (90)	< 0.0001	
MV	92 (46)	21 (17)	71 (91)	< 0.0001	28.4 (8.7–9.3) [< 0.0001]
Nosocomial pneumonia	69 (60)	25 (43)	44 (76)	0.001	
Inadequate empirical treatment	66 (42)	32 (35)	34 (51)	0.05	
Undiagnosed	43 (22)	31 (25)	12 (16)	0.1	

*Values given as No. (%), unless otherwise indicated.
†Univariate analysis.
‡Multivariate analysis.

who had undergone orthotopic liver transplantation, and Sternberg et al[23] observed a 16% mortality rate in renal transplant recipients. In the present study, 23 of 60 SOT patients (38%) died, with a 42% mortality rate for liver transplant patients and a 29% mortality rate for renal transplant patients (p = not significant).

Two factors related to the severity of the pulmonary complications had prognostic significance in each of the three different groups of immunosuppressed patients studied and also when the whole population of immunosuppressed patients was grouped together. The usefulness of the APACHE II score as a prognostic factor in bone marrow transplant patients already has been demonstrated,[8] and the present study confirms its utility in different groups of immunosuppressed patients. The need for MV was also a predictive factor of mortality in both the univariate and the multivariate analysis of the entire population (OR, 28.4), confirming this variable as the most important determinant of mortality. The avoidance of intubation may change the dismal prognosis associated with MV, particularly in HSCT patients.[6] In this sense, two randomized studies have shown that the early implementation of noninvasive MV in both immunocompetent and immunocompromised patients with PIs decreased the requirement of intubation and the incidence of nosocomial pneumonia, and improved the prognosis of these patients.[24,25] Based on the extremely poor prognosis associated with MV and the promising results obtained in the above-mentioned studies, it seems logical to recommend the application of noninvasive MV to immunocompromised patients with PIs once significant respiratory failure has ensued. However, although the employment of this modality of ventilation may avoid intubation in these patients, it may not be appropriate for or tolerated by all of them.[26]

A delay in establishing a specific diagnosis was a prognostic factor for the whole population of evaluated patients and also for SOT patients when the different groups of immunosuppressed patients were considered separately. Diagnostic delay is a variable with important clinical implications since it is potentially modifiable by medical intervention.[27–29] Confidence in the empirical antibiotic treatment, the unavailability of specific diagnostic technologies, or, more often, the rapid development of acute respiratory failure that precludes bronchoscopy may explain the delay in diagnosis in individual patients. In the present study, the higher mortality rate among patients in whom there was a diagnostic delay of > 5 days cannot be attributed to the time spent in performing specific diagnostic procedures (*ie*, cultures), since no differences were observed in the incidence of different infectious (*ie*, bacterial, fungal, and viral) and noninfectious complications between patients who received diagnoses before or after 5 days of evolution (data not shown). Similarly, the failure to make an early diagnosis was not a marker for a patient who was too ill to undergo bronchoscopy because diagnostic delay retained its prognostic significance when only those patients undergoing bronchoscopy were selected for the analysis. We

Table 6—*Univariate Analysis for Each Group of Immunocompromised Patients Evaluated

Variables	HSCT (n = 61)			HMs (n = 79)			SOT (n = 60)		
	Survivors	Nonsurvivors	OR (95% CI) [p Value]	Survivors	Nonsurvivors	OR (95% CI) [p Value]	Survivors	Nonsurvivors	OR (95% CI) [p Value]
Prophylactic antibiotic treatment	24 (83)	29 (91)	[0.3]	30 (54)	15 (65)	[0.24]	12 (32)	15 (65)	4 (1.3–11.7) [0.013]
APACHE II score > 20	2 (7)	23 (72)	34 (6.7–176) [< 0.0001]	11 (20)	19 (83)	19.4 (5.5–68.7) [< 0.0001]	4 (11)	19 (83)	39 (8.7–175) [< 0.0001]
Delay in diagnosis > 5 d	13 (59)	18 (72)	[0.2]	19 (50)	11 (58)	[0.4]	9 (29)	13 (59)	3.5 (1.2–11.2) [0.02]
Acute onset of PI	15 (60)	21 (84)	[0.06]	27 (71)	17 (85)	[0.24]	27 (82)	22 (100)	1.8 (1.4–2.3) [0.04]
Bilateral infiltrates in chest radiograph	11 (38)	26 (81)	7 (2.2–22.7) [0.001]	30 (54)	11 (48)	[0.6]	15 (40)	13 (56)	[0.2]
Infectious etiology	12 (55)	21 (84)	4.3 (1.1–17) [0.028]	25 (66)	18 (95)	9.3 (1.1–78.2) [0.017]	20 (64)	20 (91)	5.5 (1.1–28) [0.028]
MV	1 (3)	29 (91)	270 (27–760) [< 0.0001]	6 (11)	19 (83)	39.5 (10–156) [< 0.0001]	14 (38)	23 (62)	2.6 (1.7–4) [< 0.0001]

*Values given as No. (%), unless otherwise indicated.

believe that early diagnosis using different noninvasive and bronchoscopic techniques potentially could improve the prognosis of these patients. Although there are patients with severe hypoxemia in whom it may not be safe or feasible to perform a bronchoscopy, a recent study by Hilbert et al[30] has shown that the application of a laryngeal mask in airways is a safe and effective alternative to intubation for accomplishing bronchoscopy with BAL in immunocompromised patients with suspected pneumonia and severe hypoxia. Surprisingly, the delay in establishing a specific diagnosis was not a prognostic factor for all the groups of immunosuppressed patients when they were evaluated separately, and it remained significant only in the SOT group. This does not imply that trying to get an early diagnosis for PIs in HSCT patients or in those with HMs is unhelpful. These two latter groups of patients often are treated with empirical antibiotics as a diagnostic strategy is developed. Furthermore, an intense immunosuppression may accelerate the course of the pulmonary disease in that a cutoff point of 5 days might be too late to find significant differences between survivors and nonsurvivors. The fact that patients with an acute presentation of the PI (*ie*, < 7 days) had a higher mortality rate (Tables 5 and 6) further emphasizes the importance of designing strategies aimed at obtaining an early diagnosis in immunocompromised patients. The potential benefits of a bronchoscopic evaluation performed immediately after the identification of a PI to achieve early diagnosis must be evaluated in properly designed studies.

Although it was confirmed only for the HM group in the multivariate analysis, it is interesting that the univariate analyses performed in the three groups of immunocompromised patients separately showed that patients with infectious etiologies of their PIs had worse prognoses.[31] This further supports the relevance of obtaining a specific diagnosis, not only to offer a specific treatment, but also for prognostic purposes. Another finding that further emphasizes the need for obtaining a specific diagnosis is the prognostic relevance of an inadequate empirical treatment. The prognostic significance of an inadequate empirical treatment also has been evidenced by other authors evaluating patients with nosocomial pneumonia.[11,12] In almost 42% of the patients with a specific diagnosis, the empirical treatment did not cover the concrete etiology causing the PI. This variable had prognostic significance in the univariate analysis of the whole population and was particularly worrisome for patients with an infectious etiology since it carried a mortality rate of 64%, while the mortality rate was only 21% among patients with noninfectious origins of their PIs ($p < 0.02$). The inadequacy of the empirical antibiotic treatment was

Table 7—*Prognostic Factors in Relation to the Specific Immunosuppressive Condition

Variables	HSCT	HMs	SOT
Infectious etiology		15.6 (1.1–218) [0.041]	
Delay in diagnosis > 5 d			9.8 (0.9–104) [0.057]
APACHE II score > 20		7.6 (1.3–45.2) [0.026]	35 (3.5–350) [0.002]
MV	241.5 (20.3–2861.5) [< 0.0001]	15.2 (2.7–86.7) [0.002]	

*Values given as OR (95% CI) [p value].

attributable mostly to infections by Aspergillus spp, viruses, methicillin-resistant *Staphylococcus aureus*, multiresistant Gram-negative bacilli, and mycobacterium. Finally, receiving prophylactic antibiotic treatment prior to the appearance of the PI had prognostic implications in SOT patients. This variable is a well-known factor predisposing patients to lung infections by multiresistant microorganisms, and it underlines the importance of establishing a judicious antibiotic policy.[19]

The present study has limitations that have to be considered for the interpretation of the results. This was a noncontrolled observational study that evaluated different groups of immunocompromised patients. Although the total number of patients evaluated was rather high, the number of patients in any of the three groups might be insufficient to identify certain variables as being relevant for outcome.

In summary, we have described the mortality rate and have analyzed the prognostic factors of a large series of immunocompromised patients with PIs. Of these factors, MV requirement, a high APACHE II score at the onset of the pulmonary complication, and a diagnostic delay of > 5 days are associated with a high mortality rate when the population is studied as a whole. The use of methods aimed at achieving the early diagnosis of PIs is recommended to try to decrease the high mortality rate observed in this population.

References

1 Poe RH, Wahl GW, Qazi R, et al. Predictors of mortality in the immunocompromised patients with pulmonary infiltrates. Arch Intern Med 1986; 146:1304–1308

2 Baughman RP. The lung in the immunocompromised patient: infectious complications; part 1. Respiration 1999; 66:95–109

3 Tamm M. The lung in the immunocompromised patient: infectious complications; part 2. Respiration 1999; 66:199–207

4 Crawford SW. Non-infectious lung disease in the immunocompromised host. Respiration 1999; 66:385–395

5 Rubenfeld GD, Crawford SW. Withdrawing life support from mechanically ventilated recipients of bone marrow transplants: a case for evidence-based guidelines. Ann Intern Med 1996; 125:625–633

6 Nichols DJ, Maziarz RT, Haupt MT. Mechanical ventilation in hematopoietic stem cell transplant recipients: is there need for reevaluation? Chest 1999; 116:857–859

7 Rañó A, Agustí C, Jiménez P, et al. Pulmonary infiltrates in non-HIV immunocompromised patients: a diagnostic approach using non-invasive and bronchoscopic procedures. Thorax 2001; 56:379–387

8 Shorr AF, Moores LK, Edenfield WJ, et al. Mechanical ventilation in hematopoietic stem cell transplantation. Chest 1999; 116:1012–1018

9 Crawford SW, Petersen FB. Long-term survival from respiratory failure after bone marrow transplantation for malignancy. Am Rev Respir Dis 1992; 145:510–514

10 White P, Bonacum JT, Miller CB, et al. Utility of fiberoptic bronchoscopy in bone marrow transplant patients. Bone Marrow Transplant 1997; 20:681–687

11 Kollef MH, Ward S, Sherman J, et al. Inadequate treatment of nosocomial infections is associated with certain empiric antibiotic choices. Crit Care Med 2000; 28:3456–3464

12 Ibrahim EH, Ward S, Sherman G, et al. Experience with a clinical guideline for the treatment of ventilator-associated pneumonia. Crit Care Med 2001; 29:1109–1115

13 Mayaud C, Cadranel J. A persistant challenge: the diagnosis of respiratory disease in the non-AIDS immunocompromised host. Thorax 2000; 55:511–517

14 Heussel CP, Kauczor HU, Heussel GE, et al. Pneumonia in febrile neutropenic patients and in bone marrow and blood stem-cell transplant recipients: use of high-resolution computed tomography. J Clin Oncol 1999; 17:796–805

15 Murray PR, Washington JA. Microscopic and bacteriologic analysis of expectorated sputum. Mayo Clin Proc 1975; 50:339–344

16 Knauss W, Draper EA, Wagner DP, et al. APACHE II: a severity of disease classification system. Crit Care Med 1985; 13:818–829

17 Hasse JM. Nutritition assessment and support of organ transplant recipients. JPEN J Parenter Enteral Nutr 2001; 25:120–131

18 Pannutti C, Gingrich R, Pfaller MA, et al. Nosocomial pneumonia in patients having bone marrow transplant: attributable mortality and risk factors. Cancer 1992; 69:2653–2662

19 Rello J, Torres A, Ricart M, et al. Ventilator-associated pneumonia by *Staphylococcus aureus*: comparison of methicillin-resistant and methicillin-sensitive episodes. Am J Respir Crit Care Med 1994; 150:1545–1549

20 Ewig S, Torres A, Riquelme R, et al. Pulmonary complications in patients with haematological malignancies treated at a respiratory ICU. Eur Respir J 1998; 12:116–122

21 Ewig S, Glasmacher A, Ulrich B, et al. Pulmonary infiltrates in neutropenic patients with acute leukaemia during chemotherapy: outcome and prognostic factors. Chest 1998; 114: 444–451

22 Torres A, Ewig S, Insausti J, et al. Etiology of microbial patterns of pulmonary infiltrates in patients with orthotopic liver transplantation. Chest 2000; 117:494–502

23 Sternberg IR, Baughman RP, Dohn MN, et al. Utility of bronchoalveolar lavage in assessing pneumonia in immunosuppressed renal transplant recipients Am J Med 1993; 95:358–364
24 Hilbert G, Gruson D, Vargas F, et al. Noninvasive ventilation in immunocompromised patients with pulmonary infiltrates, fever, and acute respiratory failure. N Engl J Med 2001; 344:481–487
25 Antonelli M, Conti G, Rocco M, et al. A comparison of noninvasive positive-pressure ventilation and conventional mechanical ventilation in patients with acute respiratory failure. N Engl J Med 1998; 339:429–435
26 Delclaux C, L'Her E, Alberti C, et al. Treatment of acute hypoxemic nonhypercapnic respiratory insufficiency with continuous positive airway pressure delivered by a face mask: a randomized controlled trial. JAMA 2000; 284:2352–2360
27 Heath CH, Grove DI, Looke DF. Delay in appropiate therapy of Legionella pneumonia is associated with increased mortality. Eur J Clin Microbiol Infect Dis 1996; 15:286–290
28 Elizaga J, Olavarria E, Apperley JF, et al. Parainfluenza virus 3 infection after stem cell transplant: relevance to outcome of rapid diagnosis and ribavirin treatment. Clin Infect Dis 2001; 32:413–418
29 Aisner J, Schimpff SC, Wiernik PH. Treatment of invasive aspergillosis: relation to early diagnosis and treatment to response. Ann Intern Med 1977; 89:539–543
30 Hilbert G, Gruson D, Vargas F, et al. Bronchoscopy with bronchoalveolar lavage via the laringeal mask airway in high-risk hypoxemic immunosuppressed patients. Crit Care Med 2001; 29:249–255
31 Keenan HT, Bratton SL, Martin LD, et al. Outcome of children who require mechanical ventilatory support after bone marrow transplantation. Crit Care Med 2000; 28: 830–835

Prognostic Factors of Non-HIV Immunocompromised Patients With Pulmonary Infiltrates *

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