NONINVASIVE VENTILATION IN IMMUNOSUPPRESSED PATIENTS WITH PULMONARY INFILTRATES, FEVER, AND ACUTE RESPIRATORY FAILURE

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ABSTRACT

Background Avoiding intubation is a major goal in the management of respiratory failure, particularly in immunosuppressed patients. Nevertheless, there are only limited data on the efficacy of noninvasive ventilation in these high-risk patients.

Methods We conducted a prospective, randomized trial of intermittent noninvasive ventilation, as compared with standard treatment with supplemental oxygen and no ventilatory support, in 52 immunosuppressed patients with pulmonary infiltrates, fever, and an early stage of hypoxemic acute respiratory failure. Periods of noninvasive ventilation delivered through a face mask were alternated every three hours with periods of spontaneous breathing with supplemental oxygen. The ventilation periods lasted at least 45 minutes. Decisions to intubate were made according to standard, predetermined criteria.

Results The base-line characteristics of the two groups were similar; each group of 26 patients included 15 patients with hematologic cancer and neutropenia. Fewer patients in the noninvasive-ventilation group than in the standard-treatment group required endotracheal intubation (12 vs. 20, P=0.03), had serious complications (13 vs. 21, P=0.02), died in the intensive care unit (10 vs. 18, P=0.03), or died in the hospital (13 vs. 21, P=0.02).

Conclusions In selected immunosuppressed patients with pneumonitis and acute respiratory failure, early initiation of noninvasive ventilation is associated with significant reductions in the rates of endotracheal intubation and serious complications and an improved likelihood of survival to hospital discharge. (N Engl J Med 2001;344:481-7.)

THE number of immunosuppressed patients is growing. Pulmonary complications are an important cause of illness in such patients and contribute substantially to the mortality associated with various types of immunosuppression.[1,2] Patients in whom respiratory failure develops often require intubation and mechanical ventilatory assistance. Endotracheal intubation is associated with numerous complications,[3,4] and in immunosuppressed patients, mechanical ventilation is associated with a significant risk of death.[5-7]

Data on the efficacy of noninvasive ventilation in immunosuppressed patients with hypoxemic acute respiratory failure are very limited and are derived from studies involving the continuous use of noninvasive ventilation.[8,9] We hypothesized that the intermittent use of noninvasive ventilation at an early stage of hypoxemic acute respiratory failure would reduce the need for endotracheal intubation and the incidence of complications. In a prospective, randomized, controlled study, we compared the efficacy of noninvasive ventilation delivered intermittently through a face mask with that of standard medical treatment with supplemental oxygen and no ventilatory support in patients with immunosuppression from various causes in whom hypoxemic acute respiratory failure had been precipitated by pulmonary infiltrates and fever.

METHODS

Study Design and Selection of Patients

The experimental protocol was approved by the institutional review board of the hospital, and all patients or the next of kin provided written informed consent. From May 1998 through December 1999, consecutive immunosuppressed patients who were transferred to our 16-bed intensive care unit and who had clinical manifestations of pulmonary infiltrates, fever, and hypoxemic acute respiratory failure were enrolled in the study. The immunosuppression could have been caused by neutropenia (defined as a polymorphonuclear leukocyte count of less than 1000 cells per cubic millimeter of blood) after chemotherapy or bone marrow transplantation in patients with hematologic cancers, drug-induced immunosuppression in organ-transplant recipients or as a result of corticosteroid or cytotoxic therapy for a nonmalignant disease, or the acquired immunodeficiency syndrome.

The criteria for eligibility were as follows: a clinical history of pulmonary infiltrates and fever, as evidenced by a temperature of more than 38.3°C, the finding of persistent pulmonary infiltrates on radiographs, and a deterioration in pulmonary gas exchange (leukocytosis and purulent tracheobronchial secretions were not required for enrollment, because most patients had hematologic cancers and neutropenia); severe dyspnea at rest; a respiratory rate of more than 30 breaths per minute; and a ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen (PaO_2:FiO_2) of less than 200 while the patient was breathing oxygen through a Venturi mask.

The exclusion criteria were a requirement for emergency intubation for cardiopulmonary resuscitation or as a result of respiratory arrest or a rapid deterioration in neurologic status (defined as a score on the Glasgow Coma Scale of 8 or less)[10]; hemodynamic instability, defined as a systolic blood pressure of less than 80 mm Hg or evidence on electrocardiography of ischemia or clinically significant ventricular arrhythmias; chronic obstructive pulmonary disease, defined according to the standard criteria of the American Thoracic Society[11]; respiratory failure of cardiac origin, as established by physical signs and findings on chest x-ray films and echocardiograms; a partial pressure of arterial carbon dioxide of more than 55 mm Hg, with acidosis (defined as a pH of less than 7.35); recent failure of more than two organs[12]; uncorrected bleeding di-

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athesis; and tracheotomy, a facial deformity, or a recent history of oral, esophageal, or gastric surgery.

Patients were randomly assigned to receive either standard treatment without mechanical ventilation or standard treatment plus noninvasive ventilation delivered through a face mask. Randomization was performed with the use of sealed envelopes at an early stage of the respiratory failure, well before there was any need for intubation. Three sets of envelopes were provided, one for each type of immunosuppression. To minimize the risk of bias resulting from the obvious difficulty of maintaining blinding in the study, both groups were treated by the same members of the medical, nursing, and respiratory-therapy staffs and the medical management of the acute respiratory failure was similar in both groups.

Standard Treatment

Patients who were assigned to the standard-treatment group received oxygen through a Venturi mask. The rate of administration of oxygen was adjusted to achieve a level of arterial oxygen saturation (measured by oximetry) above 90 percent. In all patients, the heart rate and respiratory rate were monitored continuously, and arterial oxygen saturation was monitored continuously with a bedside pulse oximeter (Oxisensor, Nellcor, Hayward, Calif.). The head of the bed was kept elevated at a 45-degree angle. Medications included antimicrobial agents, diuretics, bronchodilators, immunosuppressive agents, and subcutaneous heparin. Parenteral nutrition was given, fluids were administered to maintain volume, and electrolyte abnormalities were corrected.

Blood cultures, an evaluation of sputum (if a sample could be obtained), and serologic tests were performed in febrile patients. Bronchoscopy with bronchoalveolar lavage was performed on the third day of empirical antimicrobial treatment in patients whose temperature did not decrease, who had clinical and radiologic evidence of pulmonary infiltrates and fever, and who had worsening of gas exchange. The fluid obtained was pooled, divided, and immediately sent to microbiology laboratories for analysis and cultures. Analysis of bronchoalveolar-lavage fluid was performed as previously described.[13]

Noninvasive Ventilation

Patients who were assigned to the noninvasive-ventilation group received the same treatment as the patients in the standard-treatment group, with the addition of periods of noninvasive ventilation. Noninvasive ventilation was delivered to the patient through a full-face mask (La Cigogne, Pessac, France).[14,15] The mask was adjusted and connected to a ventilator (Evita, Dräger, Lübeck, Germany) set in the pressure-support mode. After the mask had been secured, the level of pressure support was progressively increased and adjusted for each patient to obtain an expired tidal volume of 7 to 10 ml per kilogram of body weight and a respiratory rate of fewer than 25 breaths per minute. Positive end-expiratory pressure (PEEP) was repeatedly increased by 2 cm of water, up to a level of 10 cm of water, until the FiO_2 requirement was 65 percent or less. The FiO_2 was adjusted to maintain the arterial oxygen saturation above 90 percent. Ventilator settings were adjusted on the basis of continuous monitoring of arterial oxygen saturation, clinical data, and measurements of arterial-blood gases.

Periods of noninvasive ventilation lasted at least 45 minutes and alternated every 3 hours with periods of spontaneous breathing.[14-16] Between periods of ventilation, patients breathed oxygen spontaneously while arterial oxygen saturation was continuously monitored. Noninvasive ventilation was automatically resumed when the arterial oxygen saturation was less than 85 percent or when dyspnea worsened, as evidenced by a respiratory rate of more than 30 breaths per minute. Noninvasive ventilation was stopped if the respiratory rate was less than 25 per minute and the PaO_2:FiO_2 exceeded 200 for a period of 24 hours. Therapy was considered to be a success if intubation was not needed and the patient was transferred from the intensive care unit to another part of the hospital.

Criteria for Intubation

Patients in whom standard treatment or noninvasive ventilation was not successful underwent endotracheal intubation and received mechanical ventilation. The predetermined criteria were as follows: failure to maintain a PaO_2:FiO_2 of more than 85, the development of conditions necessitating endotracheal intubation to protect the airways (a seizure disorder or severe encephalopathy with a score on the Glasgow Coma Scale of 8 or less); the development of copious tracheal secretions; an increase in the partial pressure of arterial carbon dioxide accompanied by a pH of 7.30 or less; agitation requiring sedation; severe hemodynamic instability, defined as a systolic blood pressure of less than 70 mm Hg or evidence on electrocardiography of ischemia or clinically significant ventricular arrhythmias; and inability on the part of a patient who was randomly assigned to receive noninvasive ventilation to tolerate the face mask. The reasons for intubation were prospectively recorded.

The same protocols for sedation, ventilatory settings, weaning, and extubation were used in both groups for patients who required endotracheal intubation and conventional ventilation.

Outcomes and Definitions

The primary outcome variable was the need for endotracheal intubation and mechanical ventilation at any time during the study. Secondary outcome variables included the development of complications not present on admission, the length of stay in the intensive care unit, the duration of ventilatory assistance, death in the intensive care unit, and death in the hospital. Sepsis, severe sepsis, and septic shock were defined according to consensus guidelines.[17] Patients in whom pneumonia developed, as evidenced by radiographic findings of persistent new pulmonary infiltrates, hyperthermia or hypothermia, and worsening of gas exchange, underwent bronchoscopy with bronchoalveolar lavage. The methods of bronchoscopy and bronchoalveolar lavage, the laboratory procedures, and the diagnostic criteria for pneumonia have been described previously.[13]

Arterial blood gas levels were determined at base line, 45 minutes later, and every 24 hours thereafter; whenever acute respiratory failure worsened or improved in the judgment of the attending physician; and at the time of discharge from the intensive care unit. An improvement in gas exchange was defined on the basis of the ability to increase the PaO_2:FiO_2 to more than 200 or to a value that was more than 100 above the base-line value.[18] Gas exchange was evaluated within 45 minutes after entry into the study to detect any initial improvement and over time to detect sustained improvement. A sustained improvement in gas exchange was defined as the ability to maintain the improvement in PaO_2:FiO_2 until ventilation was discontinued, as confirmed by serial blood gas measurements.

For each patient, diagnostic microbiologic tests were conducted at entry into the study and during hospitalization in the intensive care unit. Twenty-four hours after admission to the intensive care unit, each patient was assigned a score on the Simplified Acute Physiology Score (SAPS II) test.[19] Scores for this test can range from 0 to 194, and higher scores indicate a higher risk of death.

Statistical Analysis

Results are given as means ±SD. Demographic and physiological characteristics of the two groups were compared with the use of Student's t-test for continuous variables and the Mantel–Haenszel extended chi-square test (except when sample sizes required the use of Fisher's exact test). Repeated-measures analysis of variance was used to compare the PaO_2:FiO_2 and partial pressure of arterial carbon dioxide values measured at base line, 45 minutes after the start of treatment, and at the termination of treatment. A P value of less than 0.05 was considered to indicate statistical significance. In addition to the chi-square and P values, relative risks and 95 percent confidence intervals were calculated for the outcome variables.

RESULTS

A total of 94 immunosuppressed patients were admitted to the intensive care unit between May 1, 1998,

and December 31, 1999. Acute hypoxemic respiratory failure associated with pulmonary infiltrates and fever was the reason for admission to the intensive care unit for 69 of these patients, 6 of whom had already undergone intubation and 3 of whom required emergency endotracheal intubation because of a deterioration in neurologic status (indicated by a score on the Glasgow Coma Scale of 8 or less) right after admission to the intensive care unit. Eight patients were not enrolled: one had chronic obstructive pulmonary disease, two had acute respiratory distress of cardiac origin, four had multiorgan failure, and one had a partial pressure of arterial carbon dioxide of more than 55 mm Hg with a pH of 7.31. Thus, 52 patients were enrolled, and 26 patients were assigned to each group. The reasons for immunosuppression are given in Table 1. The base-line characteristics of the two groups were similar (Table 1). Blood cultures were positive for staphylococcus and candida species in two patients and one patient, respectively, in the standard-treatment group and for two patients and two patients, respectively, in the noninvasive-ventilation group. There was no significant difference in medical treatment between the two groups of patients.

In the noninvasive-ventilation group, the mean values for levels of pressure support and PEEP during the study were 15±2 cm of water and 6±1 cm of water, respectively. During the first 24 hours, noninvasive ventilation was administered for a mean of 9±3 hours. Subsequently, the mean duration of noninvasive ventilation was 7±3 hours per day. The mean duration of noninvasive ventilation was 4±2 days (range, 1 to 9).

The mean changes in PaO_2:FiO_2 and partial pressure of arterial carbon dioxide are shown in Figure 1. The rates of initial and sustained improvement in PaO_2:FiO_2 and other outcomes in both groups are reported in Table 2. Twenty of the 26 patients in the standard-treatment group (77 percent) required endotracheal intubation, as compared with only 12 of the 26 patients in the noninvasive-ventilation group (46 percent, P=0.03). The mean interval between entry into the study and intubation was 51±23 hours (range, 4 to 152) among the 20 patients who required intubation in the standard-treatment group and 63± 18 hours (range, 16 to 176) among the 12 patients who required intubation in the noninvasive-ventilation group. The reasons for endotracheal intubation in the noninvasive-ventilation group and the standard-treatment group were the failure to maintain a PaO_2:FiO_2 of more than 85 in five and nine patients, respectively; an increase in the partial pressure of arterial carbon dioxide with acidosis in two and four patients, respectively; severe encephalopathy in two patients in each group; severe hemodynamic instability in two and three patients, respectively; and to control secretions in one and two patients, respectively.

The rate of death in the intensive care unit was significantly lower in the noninvasive-ventilation group than in the standard-treatment group (38 percent vs. 69 percent, P=0.03). All deaths occurred in patients who had been intubated after the failure of conventional treatment or of noninvasive ventilation. The serious complications and events leading to death are shown in Table 3. Pneumonia and sinusitis occurred only in patients who required intubation. The overall incidence of pneumonia and sinusitis related to the endotracheal tube was higher in the standard-treat-

TABLE 1. BASE-LINE CHARACTERISTICS OF THE PATIENTS.*

CHARACTERISTIC	NONINVASIVE-VENTILATION GROUP (N=26)	STANDARD-TREATMENT GROUP (N=26)
Age — yr	48±14	50±12
Male sex — no. (%)	18 (69)	19 (73)
SAPS II†	45±10	42±9
Respiratory rate — breaths/min	35±3	36±3
Heart rate — beats/min	108±16	111±14
Systolic blood pressure — mm Hg	127±19	123±17
Body temperature — °C	38.3±0.6	38.5±0.6
Microbiologic diagnosis of pneumonia — no. (%)‡	13 (50)	11 (42)
PaO_2:FiO_2	141±24	136±23
$PaCO_2$ — mm Hg	37±4	38±5
Arterial pH	7.45±0.04	7.43±0.04
White-cell count — cells/mm³		
Patients with immunosuppression from hematologic cancer and neutropenia	264±163	241±147
Patients with other types of immunosuppression	9980±5290	10,590±5730
Types of immunosuppression — no. (%)		
Hematologic cancer and neutropenia	15 (58)	15 (58)
Bone marrow transplantation	8 (31)	9 (35)
High-dose chemotherapy	7 (27)	6 (23)
Drug-induced immunosuppression	9 (35)	9 (35)
Organ transplantation	3 (12)	4 (15)
Corticosteroid therapy	4 (15)	3 (12)
Other	2 (8)	2 (8)
Acquired immunodeficiency syndrome	2 (8)	2 (8)

*Plus–minus values are means ±SD. PaO_2 denotes the partial pressure of arterial oxygen, FiO_2 the fraction of inspired oxygen, and $PaCO_2$ the partial pressure of arterial carbon dioxide.

†Scores on the new Simplified Acute Physiology Scale (SAPS II)[19] can range from 0 to 194. Higher scores indicate a higher risk of death.

‡The diagnosis of pneumonia was established by an evaluation of sputum or bronchoalveolar-lavage fluid before admission to the intensive care unit (in the case of eight patients in the noninvasive-ventilation group and seven patients in the standard-treatment group) or by evaluation of bronchoalveolar-lavage fluid in the intensive care unit. Bronchoalveolar lavage was performed in the intensive care unit in nine patients in the noninvasive-ventilation group and in eight patients in the standard-treatment group; a diagnosis of pneumonia was established in nine of these patients (five in the noninvasive-ventilation group and four in the standard-treatment group). The pathogens detected in samples from patients in the noninvasive-ventilation group and the standard-treatment group were as follows: *Staphylococcus aureus,* 2 and 2, respectively; *Pseudomonas aeruginosa,* 1 and 2; pseudomonas species, 0 and 1; Enterobacteriaceae, 2 and 1; *Haemophilus influenzae,* 1 and 0; *Legionella pneumophila,* 1 and 0; aspergillus species, 1 and 2; candida species, 2 and 1; cytomegalovirus, 2 and 1; and *Pneumocystis carinii,* 1 and 1.

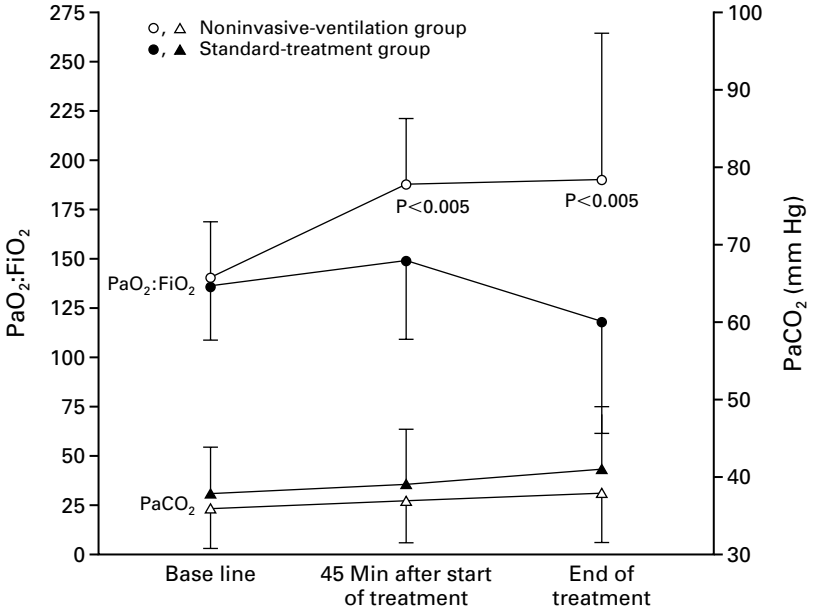

Figure 1. Mean (±SD) Changes in the Ratio of the Partial Pressure of Arterial Oxygen (PaO_2) to the Fraction of Inspired Oxygen (FiO_2) and in the Partial Pressure of Arterial Carbon Dioxide ($PaCO_2$) over Time in the 26 Patients in the Noninvasive-Ventilation Group and the 26 in the Standard-Treatment Group.

The "end of treatment" refers to the last arterial blood gas value obtained before the patient was either intubated or discharged from the intensive care unit. P values are for the comparisons with base-line values.

TABLE 2. OUTCOMES OF TREATMENT.*

OUTCOME	NONINVASIVE-VENTILATION GROUP (N=26)	STANDARD-TREATMENT GROUP (N=26)	P VALUE	RELATIVE RISK (95% CI)
Intubation — no./total no. (%)	12/26 (46)	20/26 (77)	0.03	0.60 (0.38–0.96)
Immunosuppression from hematologic cancer and neutropenia	8/15 (53)	14/15 (93)	0.02	0.57 (0.35–0.93)
Drug-induced immunosuppression	3/9 (33)	5/9 (56)	0.32	0.60 (0.20–1.79)
Immunosuppression from the acquired immunodeficiency syndrome	1/2 (50)	1/2 (50)	0.83	1.00 (0.14–7.10)
Initial improvement in PaO_2:FiO_2 — no. (%)	12 (46)	4 (15)	0.02	
Sustained improvement in PaO_2:FiO_2 without intubation — no. (%)	13 (50)	5 (19)	0.02	
Death in the ICU — no./total no. (%)†	10/26 (38)	18/26 (69)	0.03	0.56 (0.32–0.96)
Immunosuppression from hematologic cancer and neutropenia	7/15 (47)	13/15 (87)	0.02	0.54 (0.30–0.96)
Drug-induced immunosuppression	3/9 (33)	4/9 (44)	0.50	0.75 (0.23–2.44)
Immunosuppression from the acquired immunodeficiency syndrome	0/2	1/2 (50)	0.50	0.50 (0.13–2.00)
Total duration of any ventilatory assistance — days				
Among all patients	6±3	6±5	0.59	
Among survivors	5±2	3±5	0.12	
Length of ICU stay — days				
Among all patients	7±3	9±4	0.11	
Among survivors	7±3	10±4	0.06	
Death in the hospital — no./total no. (%)	13/26 (50)	21/26 (81)	0.02	0.62 (0.40–0.95)
Immunosuppression from hematologic cancer and neutropenia	8/15 (53)	14/15 (93)	0.02	0.57 (0.35–0.93)
Drug-induced immunosuppression	4/9 (44)	6/9 (67)	0.32	0.67 (0.28–1.58)
Immunosuppression from the acquired immunodeficiency syndrome	1/2 (50)	1/2 (50)	0.83	1.00 (0.14–7.10)

*Plus–minus values are means ±SD. CI denotes confidence interval, PaO_2 the partial pressure of arterial oxygen, FiO_2 the fraction of inspired oxygen, and ICU intensive care unit.

†The causes of death in the intensive care unit in the noninvasive-ventilation group and the standard-treatment group were as follows: severe sepsis or septic shock (consequent to ventilator-associated pneumonia in 1 and 2 patients, respectively) with multiorgan failure, 8 and 11; cardiogenic shock, 1 and 2; ventilator-associated pneumonia with prompt multiorgan failure, 1 and 4; and hemorrhagic shock consequent to severe gastrointestinal bleeding, 0 and 1.

TABLE 3. SERIOUS COMPLICATIONS AND COMPLICATIONS RESULTING IN DEATH IN THE INTENSIVE CARE UNIT.*

VARIABLE	NONINVASIVE-VENTILATION GROUP (N=26)	STANDARD-TREATMENT GROUP (N=26)	P VALUE
Patients with serious complications — no. (%)	13 (50)	21 (81)	0.02
Patients with complications causing death in the ICU — no. (%)	10 (38)	18 (69)	0.03
Serious complications — no. causing death in the ICU/total no. (% of group)			
Severe sepsis or septic shock†	8/8 (31)	11/12 (46)	0.26
Cardiogenic shock	1/1 (4)	2/2 (8)	0.50
Renal failure‡	0/2 (8)	0/4 (15)	0.33
Hepatic failure‡	0/5 (19)	0/7 (27)	0.51
Ventilator-associated pneumonia§	2/2 (8)	6/6 (23)	0.12
Sinusitis	0/1 (4)	0/3 (12)	0.30
Gastrointestinal bleeding	0/1 (4)	1/2 (8)	0.50

*Plus–minus values are means ±SD. Some patients had more than one serious complication. ICU denotes intensive care unit.

†Severe sepsis or septic shock was due to worsening of pneumonia present at study entry (one patient in each group), ventilator-associated pneumonia (one patient in the noninvasive-ventilation group and two in the standard-treatment group), catheter-related infections (one patient in each group), or undocumented infections (the remaining patients).

‡Renal failure was defined as a serum creatinine level of more than 2.0 mg per deciliter (179 μmol per liter), and hepatic failure as a total bilirubin level of more than 4.0 mg per deciliter (68 μmol per liter).

§Ventilator-assisted pneumonia was defined as a lower respiratory tract infection that developed after two days of mechanical ventilation. The following pathogens were detected by bronchoalveolar lavage: *Pseudomonas aeruginosa* (in three patients), *P. cepacia* (in two), acinetobacter (in one), Enterobacteriaceae (in two), and methicillin-resistant *Staphylococcus aureus* (in one). In the noninvasive-ventilation group and the standard-treatment group, ventilator-associated pneumonia was considered to have caused death in the intensive care unit as a result of septic shock in one and two patients, respectively, and the rapid onset of multiorgan failure in one and four patients, respectively. Even if multiorgan failure was multifactorial, ventilator-associated pneumonia was considered to be the primary cause of death because of the pathogenicity of the organisms involved, the occurrence of clinically significant worsening in gas exchange, and the rapid onset of multiorgan failure.

ment group than in the noninvasive-ventilation group (35 percent vs. 12 percent, P=0.05).

Noninvasive ventilation was well tolerated; no patient had gastric distention, and six patients had moderate nasal abrasions. Table 4 shows the effect on outcomes of the presence and the absence of a final diagnosis of the cause of pneumonitis with respiratory failure.

DISCUSSION

In this randomized trial, early use of noninvasive ventilation during episodes of pneumonitis and hypoxemic acute respiratory failure helped avert the need for endotracheal intubation and improved the outcomes in immunosuppressed patients. As compared with patients who were randomly assigned to receive standard treatment with supplemental oxygen, patients who were assigned to receive noninvasive ventilation had significantly lower rates of endotracheal intubation, serious complications, death in the intensive care unit, and death in the hospital.

On the basis of our previous experience, we used intermittent noninvasive ventilation[14-16] at a less advanced stage of hypoxemic acute respiratory failure than in other studies that assessed the value of noninvasive ventilation in patients who met the criteria for intubation.[8,20] In the study by Tognet et al.,[21] noninvasive ventilation was also used intermittently in patients with hematologic cancers. Ventilation delivered through a face mask can improve the pathophysiological manifestations of hypoxemic respiratory failure.[22] Our protocol of intermittent noninvasive ventilation resulted in significantly higher rates of improvement in abnormalities of gas exchange than did the standard treatment. Mechanisms of improvement may include the beneficial effects of PEEP on the redistribution of extravascular fluid, on alveolar recruitment, and in treating atelectasis at an early stage and the ability of pressure support to reduce the work of breathing and help maintain a tidal volume compatible with adequate alveolar ventilation. Reducing the work of breathing during noninvasive-ventilation sessions may also allow respiratory muscles to regain efficiency.

In the majority of patients in our study, immunosuppression was the result of hematologic cancers and neutropenia. Noninvasive ventilation enabled us to

TABLE 4. EFFECT ON OUTCOMES OF THE PRESENCE AND THE ABSENCE OF A FINAL DIAGNOSIS OF THE CAUSE OF PNEUMONITIS WITH RESPIRATORY FAILURE.*

VARIABLE	NONINVASIVE-VENTILATION GROUP				STANDARD-TREATMENT GROUP			
	FINAL DIAGNOSIS (N=17)	NO FINAL DIAGNOSIS (N=9)	P VALUE†	RELATIVE RISK (95% CI)‡	FINAL DIAGNOSIS (N=14)	NO FINAL DIAGNOSIS (N=12)	P VALUE†	RELATIVE RISK OF OUTCOME (95% CI)‡
	no. (%)				no. (%)			
Intubation	5 (29)	7 (78)	0.03	0.38 (0.17–0.85)	9 (64)	11 (92)	0.12	0.70 (0.46–1.07)
Death in the intensive care unit§	4 (24)	6 (67)	0.04	0.35 (0.13–0.93)	8 (57)	10 (83)	0.16	0.69 (0.41–1.15)
Death in the hospital	5 (29)	8 (89)	0.006	0.33 (0.15–0.72)	10 (71)	11 (92)	0.21	0.78 (0.54–1.13)

*The final diagnosis of pneumonitis was based on the results of evaluation of sputum and bronchoalveolar-lavage specimens, serologic tests, and blood cultures, as well as by the response of patients to specific therapy. A favorable response to therapy was based on an improvement in pulmonary gas exchange, fever, and findings on chest radiography. The final diagnoses of the cause of pneumonitis in the patients in the noninvasive-ventilation group and the patients in the standard-treatment group were as follows: *Staphylococcus aureus,* 2 and 1, respectively; *Pseudomonas aeruginosa,* 1 and 2; pseudomonas species, 0 and 1; Enterobacteriaceae, 2 and 1; *Haemophilus influenzae,* 1 and 0; *Legionella pneumophila,* 1 and 0; untyped bacteria that was responsive to antibiotics, 2 and 1; aspergillus species, 2 and 2; candida species, 2 and 1; Candida species plus *S. aureus,* 1 and 1; aspergillus species plus *S. aureus,* 0 and 1; cytomegalovirus, 2 and 2; and *Pneumocystis carinii,* 1 and 1.

†P values are for the comparison of patients with a final diagnosis and those without a final diagnosis.

‡CI denotes confidence interval.

§The final diagnoses for the patients in the noninvasive-ventilation group and the patients in the standard-treatment group who eventually died in the intensive care unit were as follows: *P. aeruginosa,* 0 and 1, respectively; pseudomonas species, 0 and 1; Enterobacteriaceae, 1 and 1; aspergillus species, 1 and 1; candida species plus *S. aureus,* 0 and 1; aspergillus species plus *S. aureus,* 0 and 1; and cytomegalovirus, 2 and 2.

avoid the use of intubation in 47 percent of these patients, as compared with only 7 percent of such patients in the standard-treatment group (P=0.02). The mortality rates are very high among patients with hematologic cancers who are admitted to the intensive care unit, particularly if they have neutropenia and require intubation and mechanical ventilation.[5,7,21,23-25] The risk of complications of invasive mechanical ventilation is related to the duration of ventilatory support.[26] Prospective trials have shown that the advantage of noninvasive ventilation, as compared with conventional intubation and positive-pressure ventilation, lies in its ability to prevent nosocomial pneumonia.[20,27] It is important to note that 100 percent of the patients with ventilator-associated pneumonia died in the intensive care unit both in our study and in the study by Antonelli et al.[9]

In our study, the use of noninvasive ventilation was not associated with a significantly reduced rate of death in the intensive care unit among the patients with drug-induced immunosuppression, owing perhaps to the small number of such patients and to the better outcome in general in such patients. Only four patients with the acquired immunodeficiency syndrome were enrolled, so no conclusions can be drawn with regard to the use of noninvasive ventilation in this subgroup.

Our study has several limitations. It is impossible to eliminate bias when a study cannot be blinded, and the study included only selected patients with immunosuppression who were treated in a single intensive care unit. Furthermore, the use of the failure to maintain a PaO_2:FiO_2 of more than 85 as a criterion for intubation may have led to a higher rate of intubation in the standard-treatment group because of the salutary effect of noninvasive ventilation on oxygenation. On the other hand, the exclusion of patients with a pH of less than 7.35, in addition to other reasons for exclusion, meant that the condition of the study population was relatively stable in nonrespiratory respects. All the patients in the study were transferred to our intensive care unit directly from medical wards. Some oncology units are set up as mini–intensive care units and only patients whose condition is unstable are transferred to the typical intensive care unit. Institutional variations in practice may also explain the differences in outcome between our patients and patients in other studies. Further studies are needed to refine the process of selecting patients for treatment with noninvasive ventilation.

Avoiding intubation should be an important objective in the management of respiratory failure in immunosuppressed patients, and the use of noninvasive ventilation may help achieve that goal. In selected patients with immunosuppression, pulmonary infiltrates, fever, and hypoxemic acute respiratory failure, early implementation of noninvasive ventilation was associated with a significant reduction in the rate of endotracheal intubation, serious complications, death in the intensive care unit, and death in the hospital.

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