Use of Sedatives and Neuromuscular Blockers in a Cohort of Patients Receiving Mechanical Ventilation*

Alejandro Arroliga, MD, FCCP; Fernando Frutos-Vivar, MD; Jesse Hall, MD; Andres Esteban, MD; Carlos Apezteguía, MD; Luis Soto, MD; Antonio Anzueto, MD; for the International Mechanical Ventilation Study Group†

Objective: **To describe the use of sedatives and neuromuscular blocking agents (NMBs) and their impact in outcome in an international cohort of patients receiving mechanical ventilation.**
Methods: **We analyzed the database of a prospective, multicenter cohort of 5,183 adult patients who received mechanical ventilation for > 12 h. We considered that a patient received a given agent when it was administered for at least 3 h in a 24-h period.**
Results: **A total of 3,540 patients (68%; 95% confidence interval [CI], 67 to 69%) received a sedative at any time while receiving mechanical ventilation. The median number of days of use was 3 (interquartile range [IQR], 2 to 6 days). The persistent use of sedative was associated with more days of mechanical ventilation (median, 4 days [IQR, 2 to 8 days], vs 3 days [IQR, 2 to 4 days] in patients who did not receive sedatives [p < 0.001]); more weaning days (median, 2 days [IQR, 1 to 3 days], vs 2 days [IQR, 1 to 5 days] in patients who did not receive sedatives [p < 0.001]); and longer length of stay in the ICU (median, 8 days [IQR, 5 to 15 days], vs 5 days [IQR, 3 to 9 days] in patients who did not receive sedatives [p < 0.001]). Six hundred eighty-six patients (13%; 95% CI, 12 to 14%) received an NMB for at least 1 day. The median number of days of use was 2 (IQR, 1 to 4 days). The administration of an NMB was independently related with age, a normal previous functional status, main reason of mechanical ventilation (patients with ARDS received more NMBs), and with patient management (patients requiring permissive hypercapnia, prone position, high level of positive end-expiratory pressure, and high airways pressure).**
Conclusions: **The use of sedatives is very common, and their use is associated with a longer duration of mechanical ventilation, weaning time, and stay in the ICU. NMBs are used in 13% of the patients and are associated with longer duration of mechanical ventilation, weaning time, stay in the ICU, and higher mortality.** ***(CHEST 2005; 128:496–506)***

Key words: ICU; mechanical ventilation; neuromuscular blocking agents; sedatives

Abbreviations: CI = confidence interval; IQR = interquartile range; NMB = neuromuscular blocking agent; OR = odds ratio; PEEP = positive end-expiratory pressure; SAPS = simplified acute physiology score

Sedatives, analgesics, and neuromuscular blocking agents (NMBs) are drugs commonly used in the ICU, mainly in patients requiring mechanical ventilation.[1] Sedatives and analgesics are often used to facilitate patient tolerance of invasive mechanical ventilation. The goals of sedation/analgesia in this context include decreasing pain and anxiety, reducing the stress response, and facilitating nursing care.[2,3] Studies[4–7] have suggested that we need to pay attention to the way we provide sedation/analgesia because of the potential impact on patient outcomes such as length of stay in the ICU, days of mechanical ventilation, and rate of self-extubation.

*From the Cleveland Clinic Foundation (Dr. Arroliga), Cleveland, OH; Hospital Universitario de Getafe (Drs. Frutos-Vivar and Esteban), Spain; University of Chicago (Dr. Hall), Chicago, IL; Hospital Profesor Posadas (Dr. Apezteguía), Buenos Aires, Argentina; University of Texas Health Science Center at San Antonio (Dr. Anzueto) and Instituto Nacional del Tórax (Dr. Soto), Santiago, Chile.
†For members of the Mechanical Ventilation Study Group, see the Appendix.
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Correspondence to: Antonio Anzueto MD, University of Texas Health Science Center at San Antonio, 111E, 7400 Merton Minter Blvd, San Antonio, TX 78229; e-mail: anzueto@uthscsa.edu

Furthermore, the use of sedatives and NMBs have being shown to correlate with the subsequent presence of depression and posttraumatic stress disorder symptoms[8,9] and protracted neuromuscular weakness syndromes.[10]

The current data related to the pattern of use of sedatives, analgesics, and NMBs during mechanical ventilation are limited and derived largely from mail survey reports.[11–16] Only a few studies[17–19] have tracked drug use over time, and then for brief intervals. Recently, Bertolini et al[18] reported on 2,932 patients enrolled in a multicentric study in Italy, and noted that 60% received at least one sedative during the first week in the ICU. Although 51% of the patients in the study were receiving mechanical ventilation at the time of admission to the ICU and 71% received mechanical ventilation at any time during the ICU stay, it is unclear of the type of drugs and pattern of administration in patients receiving mechanical ventilation.

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The main objective of this study is to describe the use of sedatives and NMBs in an international cohort of patients receiving mechanical ventilation. Furthermore, we want to study their impact on patient outcomes such as duration of mechanical ventilation, length of ICU stay, and length of hospital stay. We analyzed the factors associated with their use and the association with selected outcomes, such as duration of mechanical ventilation, weaning, ICU stay, and mortality.

Materials and Methods

We analyzed the database of a prospective, multicenter, international cohort of 5,183 adult patients who received mechanical ventilation for > 12 h at 361 ICUs in 20 countries.[20] The general physiologic and clinical characteristics of these patients were previously described and reported.[20] The institutional review board at each center approved the study protocol. For the purpose of this study, we collected the following information: demographic data (age, gender, simplified acute physiology score [SAPS] II), previous functional status, medical or surgical condition, date of admission to the ICU, date of initiation of mechanical ventilation, and primary indication for mechanical ventilation: acute on chronic respiratory disease (COPD, asthma, chronic pulmonary disease other than COPD), neurologic disease (coma, neuromuscular disease), or acute respiratory failure (ARDS, postoperative, congestive heart failure, aspiration, pneumonia, sepsis, trauma, cardiac arrest), date of starting weaning of mechanical ventilation, date of extubation, and date and status at discharge from the ICU.

After starting mechanical ventilation, every day for the first 28 days we recorded the use of sedatives, analgesics, and/or NMBs. We considered that a patient received one of these drugs when it was administered for at least 3 h in a 24-h period. The presence or absence of the following variables were evaluated: (1) patient management, including mode or level of ventilatory support (full support defined as ventilation with controlled volume or pressure-controlled modes or when patients received synchronized intermittent mandatory ventilation but mandatory frequency was similar to the total respiratory rate; partial support defined as ventilation with pressure support or synchronized intermittent mandatory ventilation with mandatory frequency lower than total respiratory rate; noninvasive ventilation; inverse ratio ventilation; permissive hypercapnia; prone position; and administration of inhaled nitric oxide); tidal volume (categorized as < 6 mL/kg, from 6 to 10 mL/kg, and > 10 mL/kg); applied positive end-expiratory pressure (PEEP), categorized as < 5 cm H_2O, from 5 to 10 cm H_2O, and > 10 cm H_2O; peak pressure > 50 cm H_2O; and plateau pressure > 35 cm H_2O; and (2) complications that developed over the course of the mechanical ventilation: ARDS, ventilator-associated pneumonia, sepsis, shock, acute renal failure, hepatic failure, coagulopathy, metabolic acidosis, respiratory acidosis and hypoxemia defined as a ratio of PaO_2 to fraction of inspired oxygen < 200 mm Hg. The ARDS, ventilator-associated pneumonia, and sepsis were considered as events only if they appeared > 48 h after mechanical ventilation was started. Each of these conditions has been previously defined.[20] The arterial blood gases corresponded to the values obtained once daily at approximately 8 AM. The ventilator variables corresponded to the time that the arterial blood gases were obtained.

Statistical Analysis

Data are expressed as mean (SD), median (interquartile range [IQR]), or proportions as appropriate. Continuous variables were compared with Student *t* test or Mann-Whitney *U* test if the distribution was nonparametric. Categorical variables were compared using χ^2 test or Fisher Exact Test; all p values are two-sided.

Primary outcome were use of sedatives or NMBs. To estimate the effects of multiple factors on these outcomes, a logistic regression analysis was performed using a backward stepwise selection method. The criterion for entering variables tested in the model were selected at $p < 0.10$. All variables were analyzed separately in three groups: variables previous to start mechanical ventilation (age and SAPS II were dichotomized taking as cut-off point the value that best correlated with the use of sedatives and NMBs), variables related with patient management, and complications appearing during mechanical ventilation. Significant variables ($p < 0.05$) from each group were entered to construct the final model.

Linear regression analysis was used to estimate the adjusted relation between the use of sedatives and NMBs with days of mechanical ventilation, days of weaning, and length of stay in the ICU. Similar methods were used to determine the variables associated to the use of benzodiazepines compared with propofol, taking as cohorts the patients who only received benzodiazepines or only propofol.

Results

Use of Sedatives

Of the 5,183 ICU patients admitted during the study period, 3,540 patients (68%; 95% confidence interval [CI], 67 to 69%) received a sedative at any time while receiving mechanical ventilation. For these patients, the median number of days receiving a sedative was 3 days (IQR, 2 to 6 days). Figure 1 shows the daily percentage of patients who received

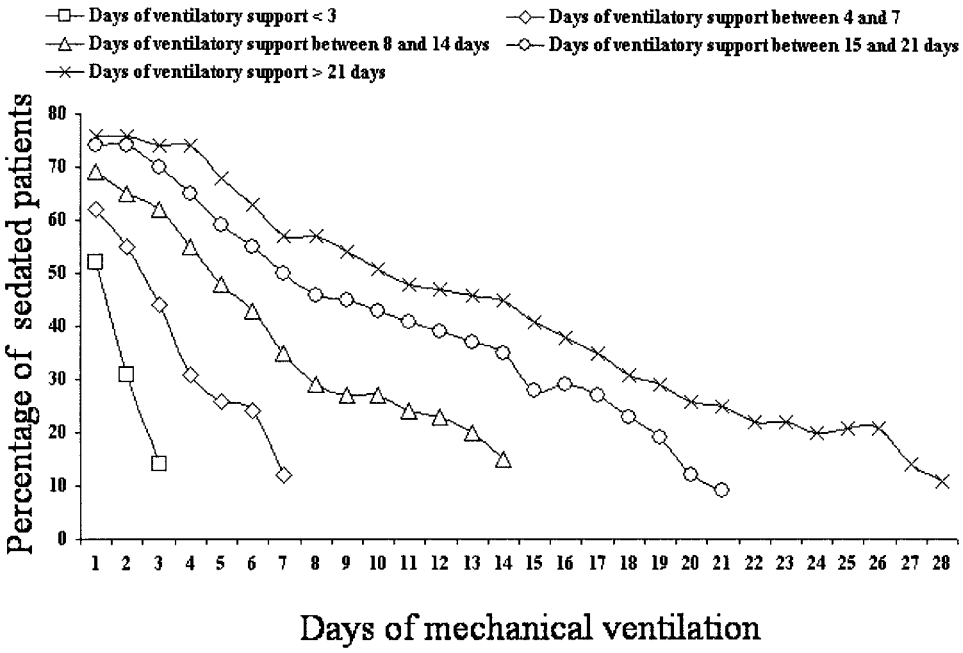

FIGURE 1. Daily use of sedatives drugs according to duration of mechanical ventilation.

a sedative according to the duration of ventilatory support. Since we registered information on sedation for 28 days, we were able to monitor 28,954 patient-days of ICU stay (96% of total). In 16,681 days of mechanical ventilation support, or 58% of the days for all patients, at least one sedative drug was administered. Benzodiazepines were administered for a total of 11,445 patients-days of ventilatory support, propofol for 3,485 patients-days of ventilatory support, and opiates for 10,491 patients-days of ventilatory support.

Most of the patients who did receive sedatives or analgesics (67.2%) received a combination of drugs. The most commonly used combinations were benzodiazepines and opiates (25%), followed by propofol and opiates (6%). Figure 2 shows the daily use of sedatives based on the duration of mechanical ventilation.

Factors Associated With the Use of Sedatives

The factors associated with sedative use are shown in Table 1. By multivariate analysis, sedatives were more likely to be administered to Europeans, men, patients aged < 50 years, and those in whom the main reason for mechanical ventilation was multiple trauma. Sedation was also independently related with the need of full ventilatory support, ventilation with a tidal volume < 6 mL/kg or > 10 mL/kg, an applied PEEP < 5 cm H_2O or > 10 cm H_2O, and the administration of an NMB. Finally, sedation was more likely to be used in patients in whom acute sepsis and shock developed over the course of mechanical ventilation.

Outcomes Associates With the Use of Sedatives

The use of sedative drugs was associated with more days receiving mechanical ventilation (median, 4 days [IQR, 2 to 8 days], vs 3 days [IQR, 2 to 4 days] in patients who did not receive sedatives [$p < 0.001$]); more weaning days (median, 2 days [IQR, 1 to 5 days], vs 2 days [IQR, 1 to 3 days] in patients who did not receive sedatives [$p < 0.001$]); and longer length of stay in the ICU (median, 8 days [IQR, 5 to 15 days], vs 5 days [IQR, 3 to 9 days] in patients who did not receive sedatives [$p < 0.001$]). After adjusting for other variables, the use of sedatives was independently related with these outcomes ($p < 0.001$). Sedated patients had a higher mortality (33% vs 26.5%), however, the use of sedatives was not independently associated with mortality (odds ratio [OR], 0.89; 95% CI, 0.75 to 1.05; $p = 0.17$)

Use of NMBs

Six hundred eighty-six patients (13%; 95% CI, 12 to 14%) received an NMB during the study period for at least 1 day. The median number of days of use of an NMB was 2 (IQR, 1 to 4 days). An NMB was administered in 2,271 days of mechanical ventilation (8% of total days of ventilatory support). Figure 3 shows the

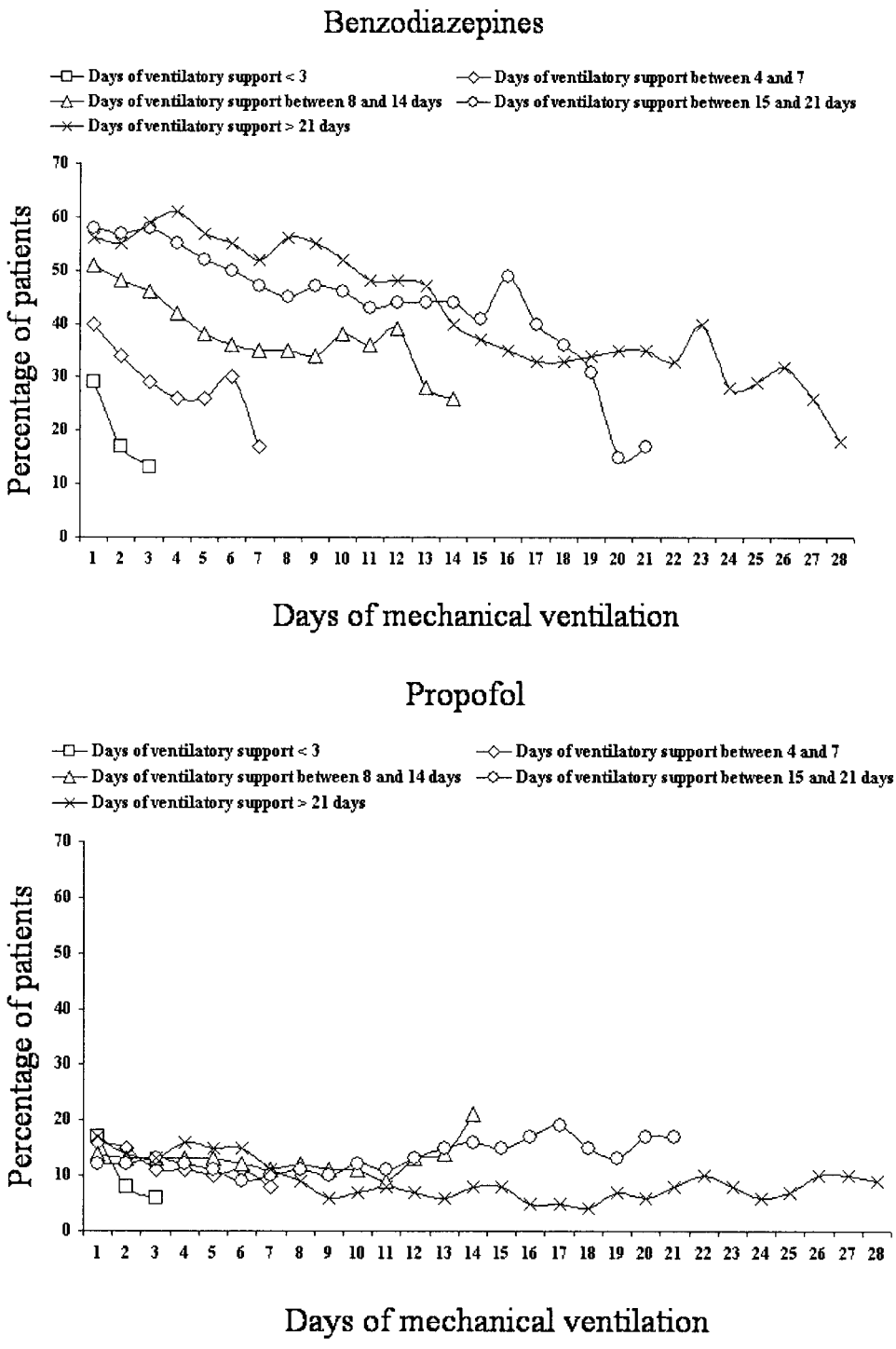

FIGURE 2. Daily use of benzodiacepines and propofol according to duration of mechanical ventilation.

daily percentage of patients receiving an NMB grouped according to the duration of mechanical ventilation.

Factors Associated With the Use of NMBs

Table 2 shows the variables associated with the daily use of NMBs. The administration of an NMB was independently related to age (more likely to be used in patients < 50 years old); gender (more common in males); a normal previous functional status; main reason of mechanical ventilation (patients with ARDS received more NMBs, while patients with coma, neuromuscular disease, and postoperative respiratory failure were less likely to receive these agents); with management strategy (patients requiring full ventila-

Table 1—*Variables Associated With Sedative Use by Univariate and Multivariate Analysis*

Variables	No.	Use of Sedatives, No. (%)	Univariate Analysis		Multivariate Analysis	
			OR	95% CI	OR	95% CI
Geographic area						
Latin America	1,222	684 (56)	1		1	
United States-Canada	1,455	987 (68)	1.65	1.42–1.94	3.60	2.77–4.67
Europe	2,506	1,869 (75)	2.30	1.99–2.67	4.97	3.75–6.58
Age, yr						
≥ 50	3,675	2,449 (66)	1		1	
50	1,508	1,085 (72)	1.30	1.13–1.45	1.30	1.04–1.64
SAPS II score						
≥ 50 points	1,759	1,151 (65)	1			
50 points	3,424	2,389 (67)	1.22	1.07–1.37		
Gender						
Female	1,985	1,267 (64)	1		1	
Male	3,198	2,273 (71)	1.39	1.23–1.56	1.31	1.08–1.61
Problem						
Medical	3,428	2,253 (66)	1		1	
Surgical	1,755	1,287 (73)	1.43	1.26–1.63	2.02	1.62–2.51
Previous functional status						
Limited activity	2,016	1,326 (66)	1			
Normal	3,167	2,214 (70)	1.20	1.07–1.37		
COPD	522	336 (64)	0.82	0.68–099		
Coma	864	472 (55)	0.49	0.42–0.57	0.47	0.36–0.62
Neuromuscular disease	94	48 (51)	0.48	0.32–0.72		
ARDS	231	201 (87)	3.24	2.19–4.78		
Postoperative acute respiratory failure	1,080	764 (71)	1.16	1.00–1.33		
Pneumonia	721	530 (73)	1.34	1.12–1.60		
Sepsis	458	375 (82)	2.23	1.74–2.85		
Trauma	407	343 (84)	2.65	2.01–3.48	1.58	1.04–2.39
Cardiac arrest	100	54 (54)	0.54	0.36–0.80		
Full ventilatory support	4,248	3,113 (73)	3.26	2.82–3.77	63.36	43.21–92.92
Partial ventilatory support	1,677	542 (32)	0.08	0.07–0.09	0.008	0.006–0.012
Tidal volume, mL/kg						
6–10	2,652	1,769 (67)	1		1	
≥ 10	1,920	1,323 (69)	1.11	0.97–1.25	1.34	1.09–1.65
≤ 6	571	498 (71)	1.25	1.02–1.52	1.49	1.07–2.08
Level of applied PEEP, cm H_2O						
5–10	1,258	623 (49)	1		1	
≤ 5	2,298	1,495 (65)	1.89	1.65–2.18	2.86	2.27–3.60
≥ 10	745	674 (90)	9.68	7.39–12.65	5.99	4.08–8.78
Noninvasive ventilation	247	74 (30)	0.18	0.14–0.24	0.22	0.14–0.35
Inverse-relation ventilation	95	88 (93)	5.96	2.75–12.89		
Permissive hypercapnia	94	89 (95)	8.45	3.43–20.84		
Prone position	72	70 (97)	16.55	4.05–67.58		
Nitric oxide inhaled	54	54 (100)				
Peak pressure 50 cm H_2O	207	172 (83)	2.35	1.62–3.39		
Plateau pressure 35 cm of water	143	128 (89)	4.07	2.38–6.97		
Use of NMBs	686	670 (98)	23.74	14.40–39.12	17.81	9.23–34.35
Barotrauma	140	116 (83)	2.28	1.47–3.56		
ARDS during mechanical ventilation	375	345 (92)	5.81	3.40–8.47	2.86	1.64–4.98
Ventilator-associated pneumonia	814	641 (79)	1.88	1.57–2.25		
Sepsis during mechanical ventilation	724	626 (86)	3.39	2.71–4.23	2.47	1.74–3.52
Shock	1,204	980 (81)	2.42	2.07–2.84	1.36	1.03–1.79
Acute renal failure	1,029	819 (80)	2.05	1.74–2.42		
Hepatic failure	340	268 (79)	1.79	1.37–2.33		
Coagulopathy	580	482 (83)	2.48	1.98–3.11		
Metabolic acidosis	428	330 (77)	1.62	1.28–2.05		
Respiratory acidosis	545	429 (79)	1.81	1.46–2.25		

tory support, permissive hypercapnia, prone position, high level of PEEP, and high airways pressure were more likely to receive an NMB); and complications during mechanical ventilation (ventilator-associated pneumonia and respiratory acidosis) were the events related with the use of NMBs.

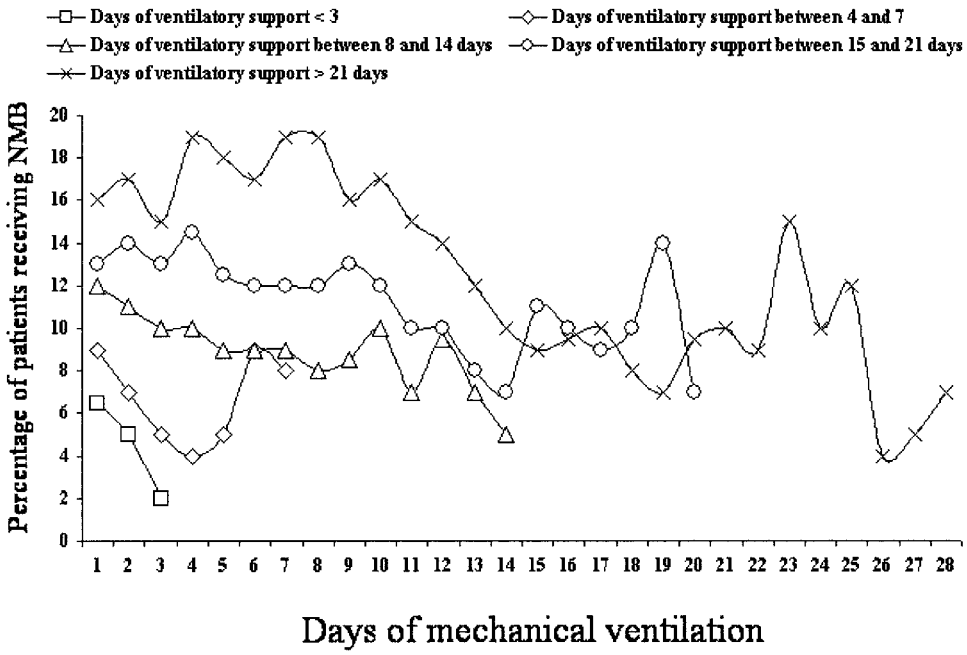

FIGURE 3. Daily use of NMBs according to duration of mechanical ventilation.

Outcomes Associated With the Use of NMBs

The use of NMBs was associated with a longer duration of mechanical ventilation (median, 7 days [IQR, 4 to 13 days], vs 3 days [IQR, 2 to 6; $p < 0.001$]); duration of weaning (median, 3 days [IQR, 1 to 6 days], vs 3 days [IQR, 1 to 4; $p < 0,001$]; and stay in the ICU (median, 10 days [IQR, 6 to 19 days], vs 7 days [IQR, 4 to 12 days; $p < 0.001$]). The mortality of patients who received NMBs was 50% (95% CI, 46 to 55%), and the use was independently related with mortality in the ICU (OR, 1.39; 95% CI, 1.08 to 1.79) [$p < 0.001$].

DISCUSSION

The main findings of this prospective, international, multicentric, observational study are as follows: (1) 68% (3,540 of 5183 patients receiving mechanical ventilation) received a sedative at any time while receiving mechanical ventilation; (2) the persistent use of sedatives was associated with more days of mechanical ventilation, more weaning days, and longer length of stay in the ICU; (3) NMBs were used in 13% (686 of 5,183 patients); and (4) patients requiring NMB has a longer duration of mechanical ventilation, weaning time, ICU stay, and higher mortality.

The use of sedatives and analgesics are very common in the ICU; however, the frequency of use of these medications is not well known. Bertolini et al[18] found that 60% of 2,932 patients admitted to 128 adult, general ICUs received a sedative or analgesic. The most common sedatives were propofol (40%) and diazepam (34%); the most common analgesics were fentanyl (36%) and morphine (22%). In their patients, the prevalence of sedation tends to decrease linearly overtime. Unfortunately no data of outcomes were described in this study. Similarly to Bertolini et al,[18] we found that 68% of our patients received a sedative at any moment during the ICU stay. Most of the patients received the sedative for a short period of time, and two thirds (67%) received a combination of drugs, more commonly benzodiazepines and opiates. Patients who received sedatives had longer time on mechanical ventilation, a longer weaning period, and a longer ICU stay.

The usage of NMBs is less known than the use of sedatives.[11,12,21–23] Small, single-institution, prospective studies[1,22,23] suggest that the rates vary between 3.4% and 15.5%. Watling et al[17] reported a survey of the use of sedatives, analgesics, and NMB in the United States. After the survey was completed, the study participants were asked to collect drug administration information for 5 consecutive days on all patients in the ICUs during the study period. Nine percent of their patients received an NMB. Unfortunately, the authors[17] did not offer information regarding the patient characteristics or concomitant therapy. Murray et al[24] did a retrospective audit of the use of NMBs in a tertiary care medical center for a 3-month period, showing that NMB use in the ICU

Table 2—*Variables Associated With NMB Use by Univariate and Multivariate Analysis*

Variables	No.	Use of NMBs, No. (%)	Univariate Analysis		Multivariate Analysis	
			OR	95% CI	OR	95% CI
Geographic area						
United States-Canada	1,455	167 (11.5)	1			
Europe	2,506	319 (13)	1.12	0.92–1.37		
Latin-America	1,222	200 (16)	1.51	1.21–1.88		
Age, yr						
≥ 50	3,675	372 (10)	1		1	
50	1,508	313 (21)	2.32	1.98–2.74	2.28	1.85–2.80
Gender						
Female	1,985	203 (10)	1		1	
Male	3,198	483 (15)	1.56	1.31–1.86	1.57	1.27–1.94
Previous functional status						
Limited activity	2,016	202 (10)	1		1	
Normal	3,167	484 (15)	1.62	1.36–1.93	1.53	1.23–1.92
COPD	522	40 (8)	0.51	0.37–0.72		
Asthma	79	19 (24)	2.10	1.01–3.55		
Coma	864	87 (10)	0.69	0.54–0.88	0.61	0.45–0.83
Neuromuscular disease	94	4 (4)	0.29	0.10–0.78	0.22	0.06–0.87
ARDS	231	87 (38)	4.39	3.32–5.80	2.01	1.43–2.83
Postoperative acute respiratory failure	1,080	98 (9)	0.60	0.58–0.75	0.65	0.49–0.86
Congestive heart failure	539	47 (9)	0.60	0.44–0.82		
Aspiration	129	27 (21)	1.76	1.14–2.72		
Pneumonia	721	144 (20)	1.80	1.47–2.21		
Sepsis	458	83 (18)	1.51	1.17–1.95		
Trauma	407	94 (23)	2.12	1.66–2.71		
Full ventilatory support	4,338	662 (15)	6.16	4.07–9.32	3.68	2.38–5.70
Inverse-relation ventilation	89	43 (48)	6.47	4.23–9.88		
Permissive hypercapnia	88	54 (61)	11.22	7.24–17.36	4.49	2.53–7.95
Prone position	66	42 (64)	12.15	7.31–20.20	4.36	2.33–8.12
Nitric oxide inhaled	47	32 (68)	14.62	7.87–27.14		
Level of applied PEEP, cm H_2O						
≤ 5	3,112	218 (7)	1		1	
5–10	757	125 (16)	2.62	2.07–3.32	1.94	1.50–2.50
≥ 10	737	239 (32)	6.37	5.18–7.83	3.06	2.39–5.70
Tidal volume, mL/kg						
6–10	2,466	272 (11)	1			
≥ 10	2,076	307 (15)	1.40	1.17–1.67		
≤ 6	641	107 (17)	1.61	1.27–2.06		
Peak pressure > 50 cm H_2O	291	93 (32)	3.40	2.62–4.42	1.46	1.04–2.06
Plateau pressure > 35 cm H_2O	186	78 (42)	5.21	3.85–7.06	2.19	1.45–3.22
Barotrauma	143	31 (22)	1.85	1.23–2.78		
ARDS during mechanical ventilation	413	123 (30)	3.17	2.52–3.98		
Ventilator-associated pneumonia	855	131 (15)	1.23	1.00–1.51	1.48	1.14–1.91
Sepsis during mechanical ventilation	742	154 (21)	1.92	1.58–2.35		
Shock	1,211	224 (18)	1.72	1.45–2.05		
Acute renal failure	1,022	176 (17)	1.49	1.23–1.79		
Coagulopathy	581	107 (18)	1.57	1.25–1.97		
Metabolic acidosis	448	76 (17)	1.38	1.06–1.79		
Respiratory acidosis	554	144 (26)	2.65	2.15–3.26	1.40	1.06–1.87

was 1.4%, mainly in patients admitted with acute respiratory failure as a reason for mechanical ventilation (9%). In our study, 13% of the patients received an NMB during the ICU stay. The use was short (median of 2 days) and was likely to be associated with severe respiratory failure, as suggested by the factors associated with their use. Contrary to the use of sedatives, there was an association with a higher mortality on univariate and multivariate analysis. We speculate that the use of an NMB is usually a final option in the management of severely ill patients, and the frequency of use is reduced when patients are treated following clinical practice guidelines.[25]

The major limitation of our study is that it is an observational study related to the use of mechanical ventilation and was not specifically design to study the usage of sedatives or NMBs. Therefore, there is

relevant information that we do not have available, such as the indications for sedation and/or NMBs, or the use of protocols for sedation and/or NMB in the participating ICUs. There are data in the literature that suggest that sedation protocols can have a significant impact on outcome.[20] However, in a survey by Rhoney and Murry,[26] only 33% of the 474 respondent reported the use of protocols for sedation in their ICUs, and 47% reported the use of protocols for NMBs.

Another limitation is that we do not have any information concerning the route of drug administration (*ie*, continuous IV infusion or intermittent bolus), doses, ways to monitor the depth of sedation, or level of neuromuscular blockade. Finally, we did not obtain information related to specific drugs sedatives and/or NMBs. Despite these limitations, the data presented in this article provide a significant insight into the patterns of usage of these drugs and their potential impact on patient outcome.

In conclusion, this study advances the knowledge of this important aspect of the care of the critically ill by describing patient characteristics and outcomes in those who receive sedatives and NMBs. This study has shown that the persistent use of sedatives is associated with longer duration of mechanical ventilation, more weaning days and, consequently, a longer length of stay in the ICU. Furthermore, patients who receive NMBs not only have a longer duration of ICU stay, but also increased mortality. We need to recognize that in order to provide patient comfort and facilitate the tolerability of mechanical ventilation, these medications need to be used, and in many circumstances the clinician has no alternatives. We believe that a prospective study specifically designed to address the issues identified in this study should be conducted in order to prospective verify our findings.

Appendix

Mechanical Ventilation Study Group

Argentina: Coordinators: C. Apezteguia, F. Palizas. R. Alasino (Hospital Municipal de Urgencias, Córdoba); R. Bastianelli (Hospital Militar, Villa Revol); J. Berón (Hospital Pablo Soria, San Salvador); C. Bevilacqua (Clínica Modelo de Morón, Morón); M. Cafaro (Hospital Regional Río Gallegos, Río Gallegos); E. Capparelli (Hospital Eva Perón, San Martín); G. Cardonatti (Hospital San Isidro, San Isidro); R. Correa (Hospital Central, Mendoza); A. Díez (Hospital Provincial del Centenario, Rosario); E. Estensoro (Hospital Escuela José de San Martín, La Plata); J. Fara (Policlínico Ferroviario, Rosario); R. Fernández (Hospital Italiano, Guaymallén); G. Fernández Cid (Hospital E. Tomú, Buenos Aires); H. Ferraro (Corporación Médica de San Martín, San Martín); A. Galaverna (Hospital Zonal Bariloche, Bariloche); C. Galleti (Sanatorio Allende, Córdoba); G. García (Hospital Clemente Álvarez, Rosario); G. Gelardi (Hospital Privado del Sur, Bahía Blanca); S. Giannasi (Hospital Italiano, Buenos Aires); R. Guidi (Hospital Italiano Garibaldi, Rosario); L. Huespe Gardel (Hospital Escuela José F. de San Martín, Corrientes); C. Irrazábal (Hospital de Clínicas José de San Martín, Buenos Aires); O. López (Sanatorio Santa Isabel, Buenos Aires); G. Menga (Hospital María Ferrer, Buenos Aires); O. Otero (Centro Oncológico de Excelencia, Gonnet); F. Pálizas (Clínica Bazterrica, Buenos Aires); P. Pardo (Sanatorio de la Trinidad, Buenos Aires); C. Plaza (Sanatorio Julio Méndez, Buenos Aires); G. Raimondi (FLENI, Buenos Aires); A. Raimondi (Sanatorio Mater Dei, Buenos Aires); E. Romero (Hospital Privado Centro Médico, Córdoba); L. de Rosa (Sanatorio Quintar, San Salvador); C. Sáez (Sanatorio Británico, Rosario); A. Sarsino (Hospital Juan A. Fernández, Buenos Aires); P. Schoon (Hospital Prof. Luis Güemes, Haedo); C. Sola (Hospital José Penna, Bahía Blanca); C. Stöltzing (Hospital Guillermo Rawson, San Juan); J. Taccone (Instituto Alfredo Lanari, Buenos Aires); C. Tolosa (Hospital Córdoba, Córdoba); M. Torreno (Sanatorio Modelo Quilmes, Quilmes); E. Turchetto (Hospital Privado de la Comunidad, Mar de Plata); R. Valenti (CEMIC, Buenos Aires); R. Vargas (Policlínico Neuquen, Neuquen); L. Vasta (Sanatorio San Patricio, Buenos Aires); L. Vázquez (Hospital Español, Godoy Cruz); Vetere (Hospital Israelita Ezrah, Buenos Aires); F. Villarejo (Hospital Prof. Alejandro Posadas, Haedo); N. Wainsztein (Hospital Privado Fundación Favaloro, Buenos Aires); O. Yunk (Hospital Español, Buenos Aires); G. Zabert (Clínica Pasteur, Neuquen).

Bolivia: Coordinator: F. Sandi Lora. L. Moya (Hospital Juan XXIII, La Paz); E. Salazar (Hospital Japonés, Santa Cruz); J.C. Zapata (Hospital Obrero, La Paz).

Brazil: Coordinator: C.M. David. S.M. Ajeje Lobo (Hosp. de Base de São José do Rio Preto, São José do Rio Preto); A.B. de Almeida (Hospital das Clínicas da Univers. Federal, Uberlândia); M.A. Braga (Hospital Biocor, Belo Horizonte); I. Buselato Chen (Hospital Nossa Senhora das Graças, Curitiba); M. Chaves Craveiro de Melo (Hospital São Lucas, Belo Horizonte); RN. Darwich (Hospital Prontocor, Belo Horizonte); C.M. David (Hospital Clementino Fraga Filho, Rio de Janeiro); R. Goldstein Alheira Rocha. (Hospital Samaritano, São Paulo); R. de Macedo Bosco (Hospital Madre Teresa, Belo Horizonte); J.M. Nogueira (Hospital Universitario São José. Belo Horizonte); E. Oliveira (Hospital Vera Cruz, Belo Horizonte); S.F. Pinto (Casa de Saúde São José, Campo Grande); S.F. Pinto (Santa Casa de Campo Grande, Campo Grande); S.F. Pinto (Univ. Fed. Mato Grosso do Sul, Campo Grande); J.L. da Rocha Paranhos (Santa Casa de Misericordia, São João del Rei); L.R. de Siqueira Musolino (Irmandade da Santa Casa de Misericordia, São Paulo).

Canada: Coordinator: T.E. Stewart. R. Fowler (Wellesley-Central Hospital, Toronto). J. Granton (Toronto Hospital General Division, Toronto); J. Granton (Toronto Hospital Western Division, Toronto); R. Hodder (Ottawa Civic Hospital, Ottawa); B. Kashin (Peel Memorial Hospital, Brampton-Ontario); S. Lapinsky (Mount Sinai Hospital, Toronto); D. Mazer (St Michael's Hospital, Toronto); R. McLean (Sunnybrook Health Sciences Centre, Toronto); T. Rogovein (St Joeseph's Health Centre, Toronto).

Chile: Coordinator: L. Soto. G. Buguedo (Hospital Pontificia Universidad Católica, Santiago); P. Hernández (Instituto Nacional del Tórax, Santiago); C. Ortega (Hospital Regional Concepción, Concepción); L. Soto (Hospital de Coquimbo, Coquimbo); L. Schölz (Hospital de Osorno, Osorno).

Colombia: Coordinator: M. González. H. Atehortua (Clínica Sta. María. Centro Cardiovascular, Medellín); C. Cadavid (Hospital Pablo Tobón Uribe, Medellín); D. Camargo (Hospital Universitario, Barranquilla); C. Dueñas (Hospital Universitario, Cartagena); A. Guerra (Hospital General, Medellín); M. Grana-

dos (Fundación Valle de Lilly, Cali); R. Panesso (Clínica Las Américas, Medellín); M.A. Perafán (Clínica Shaio, Bogotá).

Ecuador: Coordinator: J. Raad. B. Guevara (Hospital Carlos Andrade, Quito); J. Molina (Hospital Militar, Quito); J. Raad (Hospital Militar, Quito).

France: Coordinator: L. Brochard. P. Andrivet (Centre Médico-Chirurgical de Bligny, Bris-sous-Forges); D. Annane (Hôpital Raymond Poincaré, Garches); C. Arich (CHU de Nimes, Nimes); F. Baud (Hôpital Lariboisière, Paris); F. Bellenfant (Hôpital Cochin, Paris); R. Boiteau (Hôpital Louise Michel, Evry); F. Brivet (Hôpital A. Béclère, Clamart); M. Canonne (C.H.G. Les Feugrais, Elbeuf); J.P. Cardinaud (Hôpital Pellegrin-Tripode, Bourdeaux); E. Clémenti (Centre Hosp. Dept, La Roche/Yon); P. Charbonneau (C.H.U. Côte de Nacre, Caen); J. Chastre (Hôpital Bichat, Paris); R. Chauveau (C.H. André Grégoire, Montreuil-Ss-Bois); C. Chopin (CHRU - Hôpital B, Lille); J.M. Descamps (Centre Hospitalier de Niort, Niort); D. Dreyfuss (Hôpital Louis Mourier, Colombes); J.P. Faller (C. Hosp. de Belfort, Belfort); F. Fraisse (Hôpital Delafontaine, Saint-Denis); C. Girault (Hôpital Charles Nicolle, Rouen); C. Guérin (Hôpital Croix Rousse, Lyon); E. Guerot (Hôpital Boucicaut, Paris); F. Hilpert (Hôpital Ballanger, Aulnay-sous-Bois); L. Holzapfel (Centre Hospitalier, Bourg-en-Bresse); F. Jardin (Hôpital Ambroise Paré, Boulogne Vignancourt); O. Jonquet (Hôpital Gui de Chauliac, Montpellier); E. L'Her (CHU de la Cavale Blanche, Brest); Y. Lefort (Hôpital Henri Mondor, Creteil); O. Leroy (Centre Hospitalier, Tourcoing); Y. Le Tulzo (CHU Pontchaillon, Rennes); Ch. Mayaud (Hôpital Tenon, Paris); H. Mentec (Hôpital Victor Dupouy, Argenteuil); A. Mercat Hôpital Bicétre, Kremlin-Bicetre); B. Misset (Hôpital Saint-Joseph, Paris); P. Moine (Hôpital Bicêtre, Bicetre); G. Nitemberg (IGR, Villejuif); L. Papazian (Hôpital Sainte Marguerite, Marseille); A. Rabbat (Hôpital Hôtel-Dieu, Paris); T. Similowski (Hôpital Pitié Salpétrière, Paris); L. Soufir (Hôpital Saint-Louis, Paris); D. Tardy (Hôpital Saint-Camille, Bry-sur-Marne); F. Thaler (CM Chirurgical Foch, Suresnes); B. Vallet (Centre Hospitalier Univ., Lille); D. Villers (C.H.U. Nantes, Nantes); M. Wysocki (Institut Mutualiste Montsouris, Paris); J.F. Zazzo (Hôpital A. Béclère, Clamart).

Greece: Coordinator: D. Matamis. D. Georgopoulus (Heraklion University Hospital, Heraklion); M. Gianakou (Ahepa University Hospital, Thessaloniki); D. Lagonidis (Papanikolaou Hospital, Thessaloniki); G. Nakos (Ioanina University Hospital, Ioanina); K. Stavrakaki (Evangelismos Hospital, Athens); G. Thomopoulus (Laikon Hospital, Athens).

Ireland: Coordinator: G. Fitzpatrick. M. Donnelly (Adelaide and Meath Hospital, Dublin); J. Moriarty (St. James Hospital, Dublin); B. O'Sullivan (Waterford Regional Hospital, Waterford); G. Shorten (Cork University Hospital, Cork).

Italy: Coordinator: P. Pelosi. Cositi (Pol. Umberto I, Roma); G. Iapichino (Hospital S. Paolo, Milano); P. Pelosi (Policlínico, Milano); A. Pesenti (Dsp. S. Gerardo, Monza).

Mexico: Coordinator: J. Elizalde. F. Aguilera Almazán (Hospital General Regional N° 1, Chihuahua); M. Benitez Cortazar (Hospital Universitario de Puebla, Puebla); R. Carrillo Speare (Hospital PEMEX Sur, México DF); R. Castaño (Hospital de Cardiología del CMN, México DF); R. Corral (Hospital Excel. Tijuana, Baja California); D.M. D'Ector Lira (Hospital Metropolitano, México DF); G. Díaz Polanco (Hospital de Traumatología Magdalena de las Salinas, México DF); J.J. Elizalde (Hospital ABC, México DF); R. Envila Fisher (Hospital Morelos, Chihuahua); R. Envila Fisher (Hospital Clínica del Parque, Chihuahua); G. Franco G. (Hospital General de México, México DF); P. García Balbuena (Hospital General "Fernando Quiroz," México DF); O. Gayoso Cruz (Hospital Regional "Adolfo López Mateos," México DF); L. Green (Instituto Nacional de Cancerología, México DF); J.O. Herrera Hoyos (Centro Médico Las Américas, Mérida); J. Hinojosa (Hospital Angel Leaño, Guadalajara); J. Huerta (Clínica Londres, México DF); V.A. Juárez (Hospital Santelena, México DF); M. Loera (Hospital General Durango, Durango); C. López Alzate (Clínica del Mar, Mazatlán); E. López Mora (Instituto Nacional de Cardiología, México DF); S. Martínez Cano (Hospital Hidalgo Aguascalientes, Aguascalientes); R. Mendez Reyes (Hospital Regional 1° de Octubre, México DF); M. Mendoza (Hospital General de la Villa, México DF); O. Narváez Porras (Instituto Nacional de Enfermedades Respiratorias, México DF); E. Ortiz (Hospital General Irapuata, Guanajuato); A. Padua (Hospital General Torreón, Coahuila); M. Poblano (Hospital Juárez, México DF); V. Pureco Reyes (Hospital Regional "20 de Noviembre," México DF); W. Querevalum (Hospital Central Cruz Mexicana, México DF); A. Quesada (Hospital Ntra. Sra. de la Salud, San Luis Potosí); A. Ramírez Rivera (Hospital de Enfermedades Cardiovasculares y del Tórax. IMSS, Monterrey); A. Tamariz (Hospital Clínica del Centro, Chihuahua); A. Tamariz (Hospital Central Universitario, Chihuahua); A. Vargas (Hospital General de Pachuca, Pachuca); C. Vázquez (Hospital General Celaya, Guanajuato).

Peru: Coordinator: A. M. Montañez. M. Contardo (Edgardo Rebagliati Martins - UCI 7°B, Lima); E. Durand (Guillermo Almenara Irigoyen–IPPS, Lima); M. Manrique (Hospital "Jose Casimiro Ulloa," Lima); J.C. Meza (Centro Médico Naval, Lima); J. Muñoz (Edgardo Rebagliati Martins - UCI 2°C, Lima); J. Pacheco (Hospital del Apoyo "María Auxiliadora," Lima); C. Salcedo (Hosp. Nacional "Daniel Alcides Carrión," Lima); J. Silva (Hospital Central FAP, Lima); C. Torres (Hospital Nacional "Arzobispo Loayza," Lima).

Portugal: Coordinator: J. Pimentel. P. Amaro (Centro Hospitalario de Gaia, Gaia); F. Faria (Instituto Portugués de Oncología, Porto); P. Freitas (Hospital Fernando da Fonseca, Amadora-Sintra); P. Martins (Hospital Universidade, Coimbra); E. Sabino (Hospital García de Orta, Almada); J. Salcher (Hospital de San José. UUM, Lisboa); E. Silva (Hospital Senhora do Desterro, Lisboa).

Spain: Coordinators: A. Esteban, F. Frutos-Vivar. J.M. Allegre (Hospital Nuestra Señora del Rosell, Cartagena), S. Alonso (Hospital Joan XXIII, Tarragona), A. Alvarez Ruiz (Hospital General Rio Carrión, Palencia), B. Alvarez Sánchez (Hospital General, Alicante), MT Antuna (Hospital de Cabueñes, Gijón), J.M. Añón (Hospital Virgen de la Luz, Cuenca), P. Arribas (Hospital 12 de Octubre, Madrid), A. Ayensa (Hospital Virgen de la Salud, Toledo), A. Azcárate (Hospital Nuestra Señora de Aranzazu, Donostia), J. Blanco (Hospital del Río Hortega, Valladolid), G.M. Besso (Hospital Carlos Haya, Málaga), L. Cabré (Hospital de Barcelona, Barcelona), F. Carrizosa (Hospital General, Jérez de la Frontera), J. Castañeda (Hospital Clínico, Valladolid), R. de Celis (Hospital de Galdakao, Galdakao), J.A. Conesa (Hospital Clínico Universitario San Carlos, Madrid), J. Diarte (Complejo Hospitalario, Ciudad Real), A. Díaz Lamas (Complejo Hospitalario Cristal Piñor, Orense), R. Fernández (Consorci Hospitalari del Parc Taulí, Sabadell), M. Ferrer (Hospital Clinic i Provincial, Barcelona), D. Fontaneda (Hospital Virgen Blanca, León), P. Galdós (Hospital General, Móstoles), A. García Jiménez (Hospital Arquitecto Marcide, El Ferrol), J. García Pardo (Hospital Juan Canalejo, La Coruña), J. Gener (Hospital Germans Trias i Pujol, Badalona), J.A. Gómez Rubí (Hospital Virgen de la Arrixaca, Murcia), G. González Díaz (Hospital Morales Meseguer, Murcia), S. González Prado (Hospital Josep Trueta, Girona), C. Homs (Hospital General San Jorge, Huesca), J. Ibañez (Hospital Son Dureta, Palma de Mallorca), F. Jara (Hospital Mutua, Terrassa), M. León (Hospital Arnau de Vilanova, Lleida), A. Lloria (Complejo Hospitalario Rebullón, Pontevedra), J. López Díaz (Hospital La Paz, Madrid), MŞR. Lorenzo (Complejo Hospitalario Materno-Infantil, Las Palmas de Gran Canaria), S. Macías (Hospital General, Segovia),

J.A. Maldonado (Hospital de la Serranía, Ronda), J. Maynar (Hospital Santiago Apostol, Vitoria), A. Moreno (Complejo Hospitalario de San Millán-San Pedro, Logroño), A. Mota (Hospital General Universitario, Elche), T. Mut (Hospital General, Castellón), M. Nolla (Hospital General de Cataluña, Sant Cugat del Vallés), F. Ortega (Hospital Universitario de Valme, Sevilla), R. de Pablo (Hospital Príncipe de Asturias, Alcalá de Henares), E. Palazón (Hospital General Universitario, Murcia), V. Parra (Hospital de Sagunto, Sagunto), A. Peral (Hospital Gregorio Marañón, Madrid), J.C. Portela (Complejo Hospitalario Xeral-Calde, Lugo), A. Ramírez (Hospital Nuestra Señora de Sonsoles, Avila), J.A. Ramos (Hospital de Poniente, El Ejido), P. Revuelta (Hospital Universitario de Canarias, La Laguna), M. Rey (Complejo Hospitalario, Santiago de Compostela), J.J. Rodrigo (Hospital Nuestra Señora del Pino, Las Palmas de Gran Canaria), J.C. Rodríguez Borregan (Hospital Marqués de Valdecilla, Santander), J.A. Rodríguez Sarria (Hospital General, Elda), A. Rubio (Hospital Ramón y Cajal, Madrid), S. Ruiz Navarro (Hospital General Ciudad de Jaen, Jaen), V. Sagredo (Hospital Virgen de la Vega, Salamanca), P. Saura (Centre Hospitalari, Manresa), M.J. Serralta (Hospital Universitario de San Juan, Alicante), J.F. Solsona (Hospital del Mar, Barcelona), F. Suárez Sipmann (Fundación Jiménez Díaz, Madrid), F. Taboada (Hospital General de Asturias, Oviedo), S. Temprano (Hospital Severo Ochoa, Leganés), J.P. Tirapu (Hospital de Navarra, Pamplona), MŞV. de la Torre (Hospital Universitario Virgen de la Victoria, Málaga), P. Ugarte (Hospital Marqués de Valdecilla, Santander), M. Valledor (Hospital de San Agustín, Avilés), I. Vallverdú (Hospital de la Santa Creu i Sant Pau, Barcelona), C. Vaquerizo (Hospital 12 de Octubre, Madrid), A. Viñuales (Hospital Lluis Alcanyis, Xátiva).

Tunisia: Coordinator: F. Abroug. A. Bchiz (Hospital F. Bached, Sousse); J. Ben Khelil (Hospital A. Mami, Ariana); S. Bern Lakhal (Hospital Rabta, Tunis); B. Bouhaja (Hospital Mongi Slim, La Marsa); H. Chelly (Hospital Fattouma Bourguiba, Sfax); S. El Atrous (Hospital Fattouma Bourguiba, Monastir); S. Ghedira (Hospital Charles Nicolle, Tunis); H. Thabet (CAMUR. Tunis).

United Kingdom: Coordinator: P. Nightingale. O. Akinpelu (Chorley & District Hospital, Chorley); D. Bardgett (Macclesfield District General Hospital, Macclesfield); A. Batchelor (Royal Victoria Infirmary, Newcastle on Tyne); R. Beale (Guy's Hospital, London); K. Burchett (Queen Elizabeth Hospital, King's Lynn); N. Coleman (North Staffordshire Royal Infirmary, Stoke on Trent); A. Conn (Wansbeck General Hospital, Ashington); D. Edbrooke (Royal Hallamshire Hospital, Sheffield); N. Fergusson (Countess of Chester Hospital, Chester); I. Grant (Rotherham District Hospital, Rotherham); K. Gunning (Addenbrooke's Hospital, Cambridge); J. Harper (Royal Liverpool University Hospital, Liverpool); D. Higgins (Southend Hospital, Westcliffe-on-Sea); D. Jayson (Southport & Formby General Hospital, Southport); R. Loveland (Wexham Park Hospital, Slough); L. Lynch (Birmingham Heartlands Hospital, Birmingham); I. Macartney (North Manchester General Hospital, Manchester); E. Major (Morriston Hospital, Swansea); S. Mousdale (Blackbum Royal Infimary, Blackburn); N. Soni (Chelsea and Westminster Hospital, London); D. Watson (Walsgrave Hospital, Walsgrave).

Uruguay: Coordinator: C. Rodrigo. H. Bagnulo (Maciel, Montevideo); C. Rodrigo (Asociación Española Primera, Montevideo); M. Rodríguez (Hospital de Paysandú, Montevideo).

United States: Coordinator: A. Anzueto. S.M. Aguayo (Atlanta VA Medical Center, Decatur); R. Alagar (Allegheny General Hospital, Pittsburgh); R.K. Albert (Denver Health Medical Center, Denver); T.K. Aldrich (Montefiore Hospital & Medical Center, Bronx); K. Amoosa (Medical College of Wisconsin, Milwaukee); N. Anandarao (New York Methodist Hospital, Brooklyn); D.C. Angus (University of Pittsburg, Pittsburgh); A.C. Arroliga (Cleveland Clinic Foundation, Cleveland); M.F. Azrieli (Jacobu Medical Center, Bronx); R.A. Balk (Medical Center –203 Jelke, Chicago); P.W. Bates (Maine Medical Center, Porthland); J.F. Beamis, Jr. (Lahey Hitchcock Medical Center, Burlington); P.E. Bellamis (Chs Dept of Medicine, Los Angeles); D.J. Bower (Atlanta VA Medical Center, Decatur); J.P. Bradley (William Beaumont Medical Center, El Paso); R.P. Byrd, Jr.(University of East Tennese, Jonesboro); V.J. Cardenas, Jr.(University of Texas Medical Branch, Galveston); L.J. Caruso (University of Florida, Gainesville); B.R. Celli (St. Elizabeths Medical Center, Boston); G. Clermon (University of Pittsburg, Pittsburgh); S.J. Coole (Carl T. Hayden VA Medical Center, Phoenix); T.A. Dillard (Commander MCHJ-MPU, Tacoma); L.E. Efferen (SUNY Health Science Center, Brooklyn); E.W. Ely, Jr.(Vanderbilt Lung Transplant Program Newline, Nashville); P. Factor (Michael Reese Hospital & Medical Center, Chicago); T.M. Fitzpatrick (Walter Reed Army Medical Ctr, Whashington); R. Fowler (Wellesley-Central, Toronto); G.N. Giacooppe, Jr. (MCHJ-MPU, Tacoma); K.K. Guntupalli (Texas Med Ctr - Ben Taub Gen Hospital, Houston); J.B. Hall (University of Chicago, Chicago); M.E. Hanley (Denver Medical Center, Denver); M.T. Haupt (Oregon Health Science University, Portland); G.B. Hayes (St. Elizabeths Medical Center, Boston); D.E. Heiselman (Akron General Medical Center, Akron); F.C. Hiller (University of Arkansas Med Science, Little Rock); J.D. Hinze (The Univesity of Texas Health Science Center at San Antonio, San Antonio); R.D. Hite (Bowman Gray School of Medicine, Winston-Salem); R.C. Hyzy (Henry Ford Hospital, Detroit); A. Jubran (Edward Hines VA Hospital, Hines); C.A. Kaplan (University of Missouri Columbia, Columbia); MS. Karetzky (Newark Beth Israel Med Ctr, Newark); S.A. Kurenhy (Truman Medical Center, KS); K.V. Leeper, Jr.(Emory University School of Medicine, Atlanta); H. Levy (University of New Mexico, Alburquerque); T. Lo (Loma Linda University, Loma Linda); M.J. Mador (Buffalo VA Medical Center, Búfalo); G.P. Marelich (University of California Davis Med Ctr, Sacramento); M.A. Matthay (University of California, San Francisco); N.R. McIntyre (Duke University Medical Center, Durham); S.A. Metter (Maine Medical Center, Portland); MS. Niederman (Winthrop Univesity Hospital, Mineola); J.R. Norman (Univesity of Mississippi Medical Center, Jackson); D.R. Oullette (Brooke Army Medical Center, Fort Sam Houston); P. Parsons (Denver Medical Center, Denver); R.G. Patel (VA Medical Center, Jackson); R.C. Perkins, II (University of Texas Health Center at Tyler, Tyler); M.E. Petrini (University of Miississippi Medical Center, Jackson); M.R. Pinsky (University of Pittsburg, Pittsburgh); A. Pohlman (Edward Hines VA Hospital, Hines); K.W. Presberg (Medical College of Wisconsin, Milwaukee); M.P. Rocha (Carl T. Hayden VA Medical Center, Phoenix); W. Rodríguez Cintron (San Juan VA Medical Center, San Juan); M.J. Rosen(Beth Israel Medical Center, NY); T.M. Roy (James Quillen College of Medicine, Mountain Home); G. Rudelfeld (Harborview Medical Center, Seattle); M.J. Rumbak (University Florida, Tampa); S.J. Ruoss (Stanford University Medical Center, Stanford); G.A. Schmidt (University of Chicago, Chicago); R.F. Schneider (Beth Israel Medical Center, NY); C.N. Sessler (Medical College of Virginia, Richmond); C.S. Shim (Jacobi Medical Center, Bronx); L. Smith (Rush-Presbyterian-St Lukes Medical Center, Chicago); C. Strange (MUSC 96 Jonathan Lucas St, Charleston); J.I. Sznajder (Michel Reese Hospital & Medical Center, Chicago); S. Tessler (Maimonides Medical Center, Brooklyn); V. Whyte (Loma Linda University, Loma Linda); L. Wilkelmeyer (Loma Linda University Medical Center MC 1521, Loma Linda); R.G. Wundering (501 Crews Wing, Memphis); M.H. Zaman (The Brookdale Hosp Med Ctr, Brooklyn); L.H. Zimmerman (San Francisco VA Medical Center, San Francisco).

Venezuela: Coordinator: G. D'Empaire. J. España (Hospital Universitario, Caracas); F. Pérez (Hospital de Clínicas, Caracas); R. Zerpa (Hospital Militar, Caracas).

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