Paresis Acquired in the Intensive Care Unit
A Prospective Multicenter Study

Bernard De Jonghe, MD
Tarek Sharshar, MD
Jean-Pascal Lefaucheur, MD, PhD
François-Jérome Authier, MD
Isabelle Durand-Zaleski, MD, PhD
Mohamed Boussarsar, MD
Charles Cerf, MD
Estelle Renaud, MD
Francine Mesrati, MD
Jean Carlet, MD
Jean-Claude Raphaël, MD
Hervé Outin, MD
Sylvie Bastuji-Garin, MD, PhD
for the Groupe de Réflexion et d'Etude des Neuromyopathies en Réanimation

Context Although electrophysiologic and histologic neuromuscular abnormalities are common in intensive care unit (ICU) patients, the clinical incidence of ICU-acquired neuromuscular disorders in patients recovering from severe illness remains unknown.

Objectives To assess the clinical incidence, risk factors, and outcomes of ICU-acquired paresis (ICUAP) during recovery from critical illness in the ICU and to determine the electrophysiologic and histologic patterns in patients with ICUAP.

Design Prospective cohort study conducted from March 1999 to June 2000.

Setting Three medical and 2 surgical ICUs in 4 hospitals in France.

Participants All consecutive ICU patients without preexisting neuromuscular disease who underwent mechanical ventilation for 7 or more days were screened daily for awakening. The first day a patient was considered awake was day 1. Patients with severe muscle weakness on day 7 were considered to have ICUAP.

Main Outcome Measures Incidence and duration of ICUAP, risk factors for ICUAP, and comparative duration of mechanical ventilation between ICUAP and control patients.

Results Among the 95 patients who achieved satisfactory awakening, the incidence of ICUAP was 25.3% (95% confidence interval [CI], 16.9%-35.2%). All ICUAP patients had a sensorimotor axonopathy, and all patients who underwent a muscle biopsy had specific muscle involvement not related to nerve involvement. The median duration of ICUAP after day 1 was 21 days. Mean (SD) duration of mechanical ventilation after day 1 was significantly longer in patients with ICUAP compared with those without (18.2 [36.3] vs 7.6 [19.2] days; $P = .03$). Independent predictors of ICUAP were female sex (odds ratio [OR], 4.66; 95% CI, 1.19-18.30), the number of days with dysfunction of 2 or more organs (OR, 1.28; 95% CI, 1.11-1.49), duration of mechanical ventilation (OR, 1.10; 95% CI, 1.00-1.22), and administration of corticosteroids (OR, 14.90; 95% CI, 3.20-69.80) before day 1.

Conclusions Identified using simple bedside clinical criteria, ICUAP was frequent during recovery from critical illness and was associated with a prolonged duration of mechanical ventilation. Our findings suggest an important role of corticosteroids in the development of ICUAP.

JAMA. 2002;288:2859-2867 www.jama.com

ACQUISITION OF NEUROMUSCULAR dysfunction after admission to the intensive care unit (ICU) has been described during the last decade. Although this condition was first reported in a patient with severe asthma who required high doses of corticosteroids and neuromuscular blocking agents,[1] neuromuscular dysfunction acquired in the ICU has also been frequently reported in patients with sepsis or multiple organ dysfunction or both.[2] Peripheral nerve conduction abnormalities have been identified by electrophysiologic examinations, leading to the label *critical illness polyneuropathy*.[3]

The incidence rate and risk factors for ICU-acquired neuromuscular disorders have been reported in prospective observational studies based on electrophysiologic or histologic examination.[4,5] In these studies, electrophysiologic abnormalities ranged from 47% to 90% of the patients,[2,6-8] and histologic abnormalities ranged from 71% to 96%.[7,9] The sample sizes of these cohorts ranged from 20 to 70 patients. However, despite the potential impact of ICU-

Author Affiliations: Réanimation Médicale, Centre Hospitalier de Poissy-Saint-Germain en Laye, Poissy, France (Drs De Jonghe and Outin); Réanimation Médicale, Hôpital Raymond Poincaré, Garches, France (Drs Sharshar and Raphaël); Service de Physiologie–Explorations Fonctionnelles (Drs Lefaucheur and Mesrati), Département de Pathologie (Dr Authier), Santé Publique (Drs Durand-Zaleski and Bastuji-Garin), Réanimation Médicale (Dr Boussarsar), and Réanimation Chirurgicale (Dr Cerf), Hôpital Henri Mondor, Créteil, France; and Réanimation Polyvalente, Hôpital Lariboisière (Dr Renaud), and Réanimation Polyvalente, Fondation-Hôpital Saint-Joseph (Dr Carlet), Paris, France. **A complete list of the members of the Groupe de Réflexion et d'Etude des Neuromyopathies en Réanimation** appears at the end of this article.
Corresponding Author and Reprints: Bernard De Jonghe, MD, Service de Réanimation Médicale, Centre Hospitalier de Poissy-Saint-Germain en Laye, 10 rue du Champ-Gaillard, 78300 Poissy, France (e-mail: bdejonghe@chi-poissy-st-germain.fr).

acquired paresis (ICUAP) on important outcomes, such as the duration of weaning from mechanical ventilation and the duration and cost of ICU stay, the incidence and severity of clinical abnormalities remain poorly understood. To our knowledge, there are no published data on the incidence and risk factors of severe clinical weakness in the general ICU population and in particular after recovery from acute illness and improvement in consciousness, when identification of paresis is particularly relevant for the clinician. The difficulty in evaluating muscle strength in ICU patients may contribute to the lack of information. The unavailability of electrophysiological examination in many ICUs and the reluctance to obtain histologic samples in practice further support the need for a bedside approach to this condition.

The objectives of this prospective, multicenter study were to assess the clinical incidence, features, risk factors, and outcome of ICUAP identified by bedside clinical examination in ICU patients during recovery from severe illness (primary objective) and to determine the electrophysiologic and histologic patterns of ICUAP (secondary objective).

METHODS

Eligibility for Clinical Neuromuscular Evaluation

The study began in March 1999. Patients were enrolled in 5 ICUs (3 medical and 2 surgical ICUs) in 3 university hospitals and 1 university-affiliated hospital for a mean duration of 8.6 months (range, 5-15 months). All consecutive patients who underwent mechanical ventilation for at least 7 days were eligible for neuromuscular evaluation. Patients were excluded if they had disease of the peripheral nervous system, bihemispheric or brainstem lesions, fewer than 2 limbs in which muscle strength could be tested, a language barrier expected to limit patient comprehension, or if they had been referred from another ICU.

After 7 days of mechanical ventilation, patients were screened daily for awakening and comprehension based on their responses to the following 5 orders: "Open (close) your eyes," "Look at me," "Open your mouth and put out your tongue," "Nod your head," and "Raise your eyebrows when I have counted up to 5." The first day that the patient responded to at least 3 of these orders on 2 consecutive evaluations at a 6-hour interval was considered day 1.

Identification of ICUAP Patients and Controls

On day 7, after persistent satisfactory awakening and comprehension were confirmed, muscle strength was evaluated using the Medical Research Council (MRC) score, a previously validated score that assesses 3 muscle groups in each of the upper and lower limbs.[10] Each muscle group score ranges from 0 (paralysis) to 5 (normal muscle strength), and the overall score from 0 to 60. In an attempt to reduce interexaminer variability, all of the investigators were trained by the same qualified neurologist (T.S.) in MRC score measurement. Because our goal was to identify patients with clinically significant weakness, patients with an MRC score less than 48 were a priori considered to have ICUAP, whereas those with an MRC score of 48 or higher, which indicates muscle strength of 5 (normal) or 4 (subnormal) in each limb segment, were considered controls.

Paraclinical Examinations in ICUAP Patients

To confirm the peripheral neuromuscular origin of the clinical weakness, all ICUAP patients underwent an electrophysiologic evaluation within 72 hours after day 7. To standardize the electrophysiologic procedure and interpretation, 2 trained electrophysiologists (J.-P.L., F.M.) performed all electrophysiologic examinations using a portable electroneuromyogram machine (Keypoint portable, Medtronic France, Boulogne-Billancourt, France). All data were centrally analyzed according to standard laboratory references.[11] The ICUAP patients with persistent paresis at day 14 underwent muscle biopsy. The histologic samples were obtained from the left quadriceps or deltoid muscles with the patient under local anesthesia. Histologic analyses were performed in the Pathology Department of Henri-Mondor Hospital. Muscle samples were processed for hematoxylin-eosin, modified Gomori trichrome, and NADH-tetrazolium reductase and cytochrome C oxidase histoenzymatic reactions using standard procedures. Muscle fiber necrosis and regeneration, muscle fiber atrophy, and neurogenic changes were defined according to histologic criteria of Dubowitz et al.[12] The ICUAP patients underwent MRC score measurement weekly during the first month and monthly during a 9-month period until the regression of paresis (MRC score $\geq$48) or death.

The study protocol was approved by the Cochin Hospital Ethics Committee (Paris, France) provided the electrophysiologic examination was performed only in ICUAP patients, muscle biopsy was performed only in ICUAP patients with delayed clinical recovery, and peripheral nerve biopsy was not performed. Informed consent was obtained from ICUAP patients or relatives.

Data Collection

Clinical factors that may influence the onset of ICUAP were selected a priori and prospectively recorded between ICU admission and awakening (day 1) for both ICUAP patients and controls. These included potential risk factors at ICU admission, metabolic abnormalities, organ dysfunction–related variables (TABLE 1), and medications (TABLE 2). For medications suspected of influencing the onset of ICUAP, we recorded the number of patients who received the drug at least once before day 1 and the total number of days of administration and cumulative dosages in patients who received the drug.

Statistical Analysis

The ICUAP patients and controls were first compared using univariate analyses. Quantitative variables were reported as mean (SD), except when

Table 1. Univariate Comparison of Baseline Characteristics, Metabolic Variables, and Organ Dysfunction–Related Variables Between Intensive Care Unit–Acquired Paresis (ICUAP) and Control Patients*

Variable	ICUAP Patients (n = 24)	Controls (n = 71)	OR (95% CI)	*P* Value†
Baseline characteristics				
Age, y	67.6 (11)	59.3 (16)	1.04 (1.0-1.09)	.02
Female sex, No. (%)	12 (50)	14 (20)	4.1 (1.5-11.1)	.004
Preexisting risk factors (≥1), No. (%)	12 (50)	23 (32)	2.1 (0.8-5.4)	.12
Diabetes mellitus	7 (29)	8 (11)	3.2 (1.0-10.4)	.05
Chronic renal failure	0 (0)	4 (6)	-	.60
Alcohol abuse	8 (33)	16 (22)	1.7 (0.6-4.8)	.29
Surgical patient, No. (%)	9 (38)	19 (27)	1.6 (0.6-4.4)	.32
Diagnosis, No. (%)			NA	NA
COPD exacerbation	4 (17)	17 (24)		
Severe heart disease	2 (8)	9 (13)		
Severe aspiration or infectious pneumonia‡	5 (21)	12 (17)		
Severe deep infection§	3 (12)	6 (8)		
Complicated abdominal disease	4 (17)	4 (6)		
Medical condition, others	4 (17)	9 (13)		
Trauma	2 (8)	14 (20)		
Admission SAPS 2‖	53.3 (13.5)	47.3 (18.5)	1.02 (0.99-1.05)	.15
Admission ODIN score¶	3.0 (0.9)	2.5 (1.3)	1.4 (0.95-2.10)	.08
Infection on admission, No. (%)	16 (67)	34 (48)	2.2 (0.8-5.8)	.11
Metabolic variables				
Lowest serum sodium, mEq/L (n = 94)	129.6 (5.7)	132.7 (5.7)	0.91 (0.84-0.99)	.03
Lowest serum potassium, mEq/L (n = 94)	2.9 (0.4)	3.6 (3.8)	0.80 (0.61-1.21)	.15
Highest blood urea nitrogen, mg/dL (n = 94)	73.3 (47.0)	47.0 (38.9)	1.04 (1.01-1.07)	.01
Highest blood creatinine, mg/dL (n = 94)	3.2 (2.5)	2.4 (2.3)	1.0 (0.99-1.0)	.16
Lowest arterial pH (n = 94)	7.23 (0.09)	7.25 (0.09)	0.25 (0.01-42.7)	.60
Lowest Pao_2, mm Hg	64.6 (19.7)	71.4 (23.8)	0.99 (0.96-1.01)	.21
Highest $Paco_2$, mm Hg	61.2 (21.9)	61.5 (24.9)	0.99 (0.98-1.02)	.96
Highest blood glucose, mg/dL (n = 93)	360.3 (142.3)	259.4 (113.5)	1.11 (1.04-1.19)	.001
Highest bilirubin, mg/dL (n = 93)	2.0 (1.9)	1.4 (1.5)	1.01 (0.99-1.03)	.14
Highest CPK, median (range), IU/L (n = 87)	405 (18-4591)	508 (1-19 600)	1.0 (0.99-1.0)	.10
Organ dysfunction–related variables				
Circulatory dysfunction, No. (%)#	21 (88)	50 (70)	2.9 (0.8-11.1)	.10
Renal dysfunction, No. (%)#	10 (42)	17 (24)	2.3 (0.8-6.1)	.10
Liver dysfunction, No. (%)#	4 (17)	7 (10)	1.8 (0.5-7.0)	.59
Hematologic dysfunction, No. (%)#	3 (12)	10 (14)	0.9 (0.2-3.5)	.84
Neurologic dysfunction, No. (%)#	9 (38)	23 (32)	1.3 (0.5-3.3)	.65
Maximal No. of simultaneous organ dysfunctions	2.8 (0.8)	2.4 (1.0)	1.2 (0.9-2.1)	.08
No. of days with dysfunction in ≥2 organs	10.3 (7.0)	4.8 (4.1)	1.21 (1.09-1.34)	<.001
Infection, No. (%)#	21 (88)	56 (79)	1.9 (0.5-7.3)	.53
Septic shock, No. (%)**	9 (38)	14 (30)	2.4 (0.8-6.8)	.09
Extrarenal replacement, No. (%)	8 (33)	9 (14)	3.4 (1.1-10.5)	.03
Duration of MV before awakening, d	16.6 (8.2)	10.8 (5.5)	1.13 (1.1-1.22)	.003
Length of ICU stay before awakening, d	17.7 (9.9)	11.3 (5.9)	1.12 (1.04-1.20)	<.001

*Baseline characteristics were recorded on ICU admission. Metabolic and organ dysfunction variables were recorded between ICU admission and awakening (day 1). The most abnormal values of the metabolic variables were recorded. Continuous data are reported as mean (SD) except when otherwise indicated. OR indicates odds ratio; CI, confidence interval; NA, not applicable; COPD, chronic obstructive pulmonary disease; SAPS, Simplified Acute Physiology Score; ODIN, organ dysfunction and/or infection; CPK, creatine phosphokinase; and MV, mechanical ventilation. To convert mg/dL to mmol/L (blood urea nitrogen), multiply by 0.357; mg/dL to μmol/L (blood creatinine), multiply by 88.4; mg/dL to mmol/L (blood glucose), multiply by 0.0555; mg/dL to μmol/L (bilirubin), multiply by 17.1.

†The *t* test or Mann-Whitney *U* test was used for means; χ^2 test or Fisher exact test was used for proportions.

‡Excluded COPD exacerbation.

§Severe pyelonephritis, mediastinitis, and cellulites.

‖SAPS II is an ICU severity score that includes 17 physiologic, demographic, and underlying disease variables recorded within 24 hours after ICU admission.[14]

¶The ODIN score assessed dysfunction in 6 organ systems: respiratory, cardiovascular, renal, hematologic, hepatic and neurologic, and infection.[15]

#Organ dysfunction was recorded according to the ODIN score definitions.[15]

**Septic shock was defined as the administration of catecholamines and a concomitant documented infection after exclusion of other causes of shock.

otherwise indicated, and were not dichotomized. Categorical variables were coded as 0 or 1. The *t* test and Mann-Whitney *U* test were used for comparison of quantitative variables; the χ^2 test and Fisher exact test were used for comparison of qualitative variables. Odds ratios (ORs) with 95% confidence intervals (CIs) were estimated separately for each variable using standard case-control methods with unconditional logistic regression models.[13] Variables, including drug exposure variables (number of patients receiving the drug, number of days of administration, and cumulative dosage) with $P<.15$ in univariate analysis, were then considered for multivariate analysis. First, a systematic search for statistical association between these variables was performed in the control patients, using correlation and regression analyses and χ^2 tests as appropriate. Second, statistically associated variables and variables with clinically suspected association were then analyzed in multiple 2×2 analyses to assess first-order interaction and confounding by fitting multiplicative models. Finally, variables identified from this selection were entered into a backward step-by-step logistic regression. $P \leq .05$ was considered statistically significant. All significance tests were 2-tailed. Data were analyzed using the BMDP software (University of California, Berkeley).

RESULTS

During the study period, 1246 patients required mechanical ventilation. Of these, 332 patients (26.6%) underwent mechanical ventilation for at least 7 days. One hundred twenty-six patients had exclusion criteria, and muscle weakness could not be evaluated in another 111 patients. Of these, 85 (76.6%) died before regaining consciousness (FIGURE 1). Thus, 95 patients (26 women and 69 men) were included in the study. Sixty-seven patients (70%) were recruited in a medical ICU and 28 (30%) in a surgical ICU. The mean (SD) age was 62.0 (15.3) years, and the Simplified Acute Physiology Score (SAPS) II[14] on admission was 48.7 (17.4). The mean delay between onset of mechanical ventilation and awakening (day 1) was 12.4 (6.8) days. In 5 patients, only 3 limbs could be tested, and in 7 patients, only 2 limbs could be tested. Twenty-four patients developed ICUAP, corresponding to an incidence rate of 25.3% (95% CI, 16.9%-35.2%).

Table 2. Univariate Comparison of Medication Variables Between Intensive Care Unit–Acquired Paresis (ICUAP) and Control Patients*

Medication Variable	ICUAP Patients (n = 24)	Controls (n = 71)	OR (95% CI)	*P* Value†
Midazolam				
No. (%) of patients	24 (100)	66 (93)	NA	.42
Total No. of days	8.2 (4.9)	6.6 (4.5)		.15
Cumulative dosage, mg (range)	1450 (10-7200)	696 (4-12 480)		.46
Aminoglycosides				
No. (%) of patients	16 (67)	30 (42)	2.7 (1.0-7.3)	.04
Total No. of days	4.9 (3.3)	4.8 (3.4)		.92
Cumulative dosage, mg (range)	590 (100-2620)	600 (150-4500)		.23
Furosemide				
No. (%) of patients	20 (83)	42 (59)	3.5 (1.1-11.3)	.03
Total No. of days	6.6 (5.6)	4.6 (3.4)		.35
Cumulative dosage, mg (range)	813 (20-7800)	280 (20-40 000)		.07
Corticosteroids				
No. (%) of patients	13 (54)	13 (18)	5.3 (1.9-14.6)	.001
Total No. of days	8.7 (7.4)	7.2 (5.5)		.60
Cumulative dosage, mg (range)	1450 (30-4150)	2300 (32-25 000)		.32
Neuromuscular blockers				
No. (%) of patients	15 (62)	29 (41)	2.4 (0.9-6.3)	.07
Total No. of days	3.3 (3.3)	2.1 (1.4)		.11
Cumulative dosage, mg (range)	13.3 (4.0-640)	16.0 (7.0-250)		.11

*Medication data were recorded between ICU admission and awakening (day 1). Numbers of days of administration are reported as mean (SD) and cumulative dosages as median. The total number of days of drug administration and cumulative dosages were calculated in patients who received the drug. For aminoglycosides, corticosteroids, and neuromuscular blockers, cumulative dosages were expressed as gentamicin-equivalent dosage, vecuronium-equivalent dosage, and hydrocortisone-equivalent dosage, respectively. OR indicates odds ratio; CI, confidence interval; and NA, not applicable.
†The *t* test or Mann-Whitney *U* test was used for continuous data; the χ^2 test or Fisher exact test was used for proportions.

Description of ICUAP Patients

The mean MRC score of the 24 ICUAP patients (extrapolated to 4 limbs when only 2 or 3 limbs could be tested) was 33.2 (11.5) (range, 8-45). The mean values of each item of the MRC score in the 24 ICUAP patients are presented in FIGURE 2. Proximal muscle strength was significantly less than distal muscle strength in both upper and lower limbs ($P<.001$). No difference was found between the right and left sides. In 2 patients, the electrophysiologic study was unreliable due to severe peripheral edema. In the other 22 patients, electrophysiologic examination revealed a sensorimotor axonal peripheral neuropathy, with a marked reduction in the amplitude of compound muscle action potentials and sensory nerve action potentials in the 4 limbs. Repetitive nerve stimulation did not reveal neuromuscular blockade. Abnormal spontaneous electromyographic activity was observed in 10 patients.

Among the 13 ICUAP patients who were still paralyzed at day 14, 2 were discharged to another hospital before muscle biopsy was performed, and muscle biopsy was not done in 1 patient. Of the 10 patients who underwent muscle biopsy, 4 had previously received both corticosteroids and neuromuscular blocking agents, 3 had received corticosteroids only, 2 had received neuromuscular blocking agents only, and 1 had not received either

drug. In all patients, histologic examination revealed primary myopathic changes (type 2 fiber atrophy with myosinolysis, n=10; muscle fiber necrosis, n=5) in addition to neurogenic muscle atrophy (n=10). Only 1 patient had an inflammatory reaction and angiopathic signs.

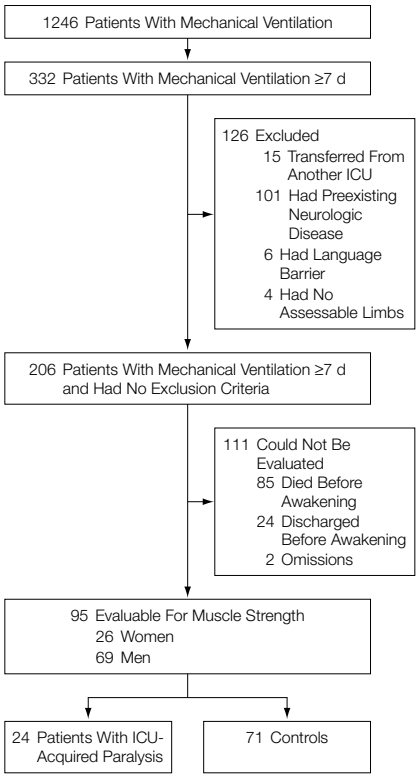
Comparison of ICUAP and Control Patients

Univariate analysis of factors suspected to influence the occurrence of ICUAP is presented in Tables 1 and 2. Among the baseline characteristics on admission, older age ($P=.02$), female sex ($P=.01$), and preexisting diabetes mellitus ($P=.05$) were significantly associated with ICUAP (Table 1). A trend toward higher SAPS II and organ dysfunction and/or infection[15] score was also observed in ICUAP patients. Among the metabolic variables, the lowest serum sodium level observed between admission and day 1 and the highest blood urea nitrogen and blood glucose levels were significantly associated with ICUAP. Analysis of variables related to organ dysfunction showed that the number of days with dysfunction in at least 2 organs and the number of days of mechanical ventilation and of ICU stay before day 1 were significantly higher in ICUAP patients than control patients. Significantly more ICUAP patients also underwent extrarenal replacement therapy. A trend toward a higher frequency of septic shock was also observed. Twenty-six (27%) of the 95 patients received corticosteroids at least once before day 1 (septic shock, n=9; chronic obstructive pulmonary disease [COPD] exacerbation, n=6; laryngeal dyspnea, n=6; organ transplantation, n=2; systemic vasculitis, n=1; non-Hodgkin lymphoma, n=1; and unclear indication, n=1). All patients received supraphysiologic dosages. None of the patients received mineralocorticoids. Corticosteroids were administered significantly more frequently in ICUAP patients than in control patients (Table 2). No relation between ICUAP and corticosteroid treatment duration or cumulative dosage was observed. Aminoglycosides and furosemide were also administered significantly more frequently to ICUAP patients, and a similar trend was observed for neuromuscular blockers.

There was no significant interaction among the 22 variables with $P<.15$ in univariate analysis. After 2×2 analyses, 11 variables were entered in the multivariate regression analysis: age, female sex, lowest serum sodium level, highest blood urea nitrogen and glucose levels, number of days with dysfunction in 2 or more organs, duration of mechanical ventilation before awakening, and administration (yes/no) of corticosteroids, aminoglycosides, furosemide, and neuromuscular blockers. After regression analysis, female sex, number of days with dysfunction in 2 or more organs, duration of mechanical ventilation before awakening, and administration of corticosteroids remained independent risk factors of ICUAP (TABLE 3). Risk estimates ranged from 1.10 to 14.90. The goodness of fit of the model was 0.92.

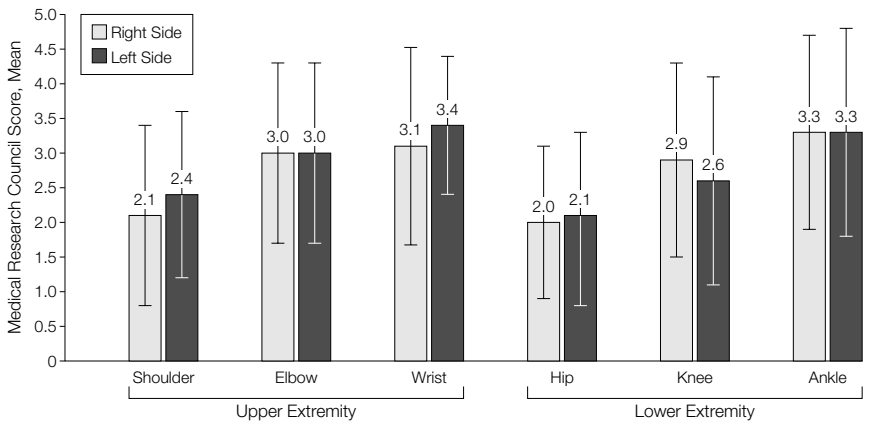
The mean (SD) total duration of mechanical ventilation was significantly longer in ICUAP patients (34.8 [37.3] days; median, 30) than in controls (18.4 [19.6] days, $P<.001$; median, 15). Spe-

Figure 1. Study Flowchart



The high number of patients excluded for preexisting neurologic disease is due to the recruitment of a large number of patients with peripheral neurologic disease on admission in 1 intensive care unit (ICU).

Figure 2. Neuromuscular Scores in Each Limb Segment in Patients With Intensive Care Unit–Acquired Paresis (ICUAP)



Mean Medical Research Council scores for each limb segment in the 24 ICUAP patients. The Medical Research Council score attributes a value between 0 (complete paralysis) and 5 (normal muscle strength) to each limb segment. Error bars represent SDs.

cifically, the duration of mechanical ventilation after awakening (day 1) was significantly longer in ICUAP patients (18.2 [36.3] days; median, 6) than in controls (7.6 [19.2] days, $P=.03$; median, 3), and a trend toward longer ICU stay after awakening was observed in ICUAP patients (27.6 [31.4] days vs 14.6 [19.6], $P=.06$; medians, 13 vs 10) (FIGURE 3). Four ICUAP patients (17%) and 4 controls (6%) died in the ICU ($P=.20$).

Table 3. Multivariate Analysis of Risk Factors for Intensive Care Unit–Acquired Paresis*

Independent Risk Factor	OR (95% CI)	*P* Value†
Female sex	4.66 (1.19-18.30)	.02
No. of days with dysfunction in ≥2 organs‡	1.28 (1.11-1.49)	<.001
Duration of mechanical ventilation§	1.10 (1.00-1.22)	.049
Corticosteroid administration	14.90 (3.20-69.80)	<.001

*Risk factors were recorded between intensive care unit admission and awakening (day 1). Variables with $P<.15$ in univariate analysis were entered into a logistic regression analysis after identification of interaction and confounding. OR indicates odds ratio; CI, confidence interval.
†Logistic regression.
‡The OR per additional day with dysfunction in 2 or more organs.
§The OR per additional day of mechanical ventilation.

Follow-up of the ICUAP Patients

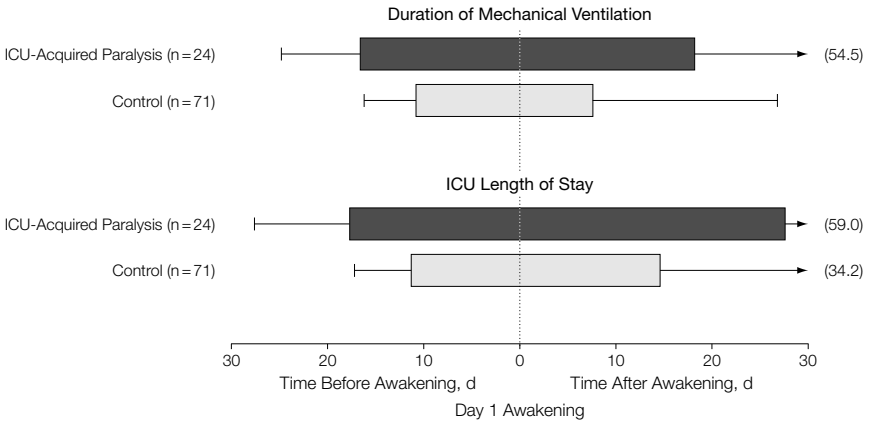
The mean duration of paresis after awakening (day 1) in ICUAP survivors was 44.6 (79.2) days, with a median duration of 21 days (FIGURE 4). No correlation was found between the initial MRC score and the duration of paresis. At the end of the 9-month follow-up period of the 24 ICUAP patients, 7 patients had died and 1 homeless patient had been lost to follow-up. Of the remaining 16 patients (67%), 12 returned home either at hospital discharge (n=3) or after further treatment in a rehabilitation center (n=9), and 4 were in a long-term care facility or retirement home. All except 1 of these patients had recovered an MRC score of 48 or higher.

COMMENT

To our knowledge, this is the first prospective study of a multicenter, general ICU cohort of patients who had undergone mechanical ventilation and in whom a neuromuscular disorder was identified using a bedside clinical approach. Clinical evaluation of motor weakness in ICU patients is challenging. Two previous prospective cohort studies that included clinical diagnostic criteria were unable to shed light on this question, because a detailed description of the clinical abnormalities was not included in one[16] and the results were not applicable to a general ICU population in the other.[17] The most important factor that limits a reliable clinical evaluation is the alteration of consciousness, which may be due to various causes, including sepsis or administration of sedatives and analgesics.[18] Because of these difficulties, numerous investigators have previously identified ICU-acquired neuromuscular disorders by systematic electrophysiologic or histologic examination after a predefined duration of stay in the ICU, regardless of the level of consciousness.[4] However, the clinical relevance of this approach is questionable given that many ICU patients die without regaining consciousness (41% of the patients without previous neuromuscular disorders requiring ≥7 days of mechanical ventilation in our study). Furthermore, the high rate of electrophysiologic or histologic abnormalities, which has reached 100% in some studies,[7,8,19] raises questions about the discriminatory value of these tests in identifying patients with clinically significant neuromuscular disorders.

Our focus on the ICU patients who regained normal or almost normal consciousness has several advantages. First, awakening is a clinically important event during ICU stay, because this is usually the starting point of the process that will lead to weaning from the ventilator and to progressive recovery. Identification of a peripheral neuromuscular abnormality that might interfere with this recovery process is the cornerstone in patients who regain consciousness after septic, ischemic, or drug-related encephalopathy. Second, return to normal or almost normal consciousness and comprehension allows all patients to undergo clinical assessment using simple bedside tests, such as limb muscle strength evaluation. This is especially important because electrophysiologic and histologic examinations are often difficult to perform in most ICUs and may be considered too invasive.

Figure 3. Comparison of Mechanical Ventilation and Intensive Care Unit (ICU) Length of Stay Between Patients With ICU-Acquired Paresis and Controls



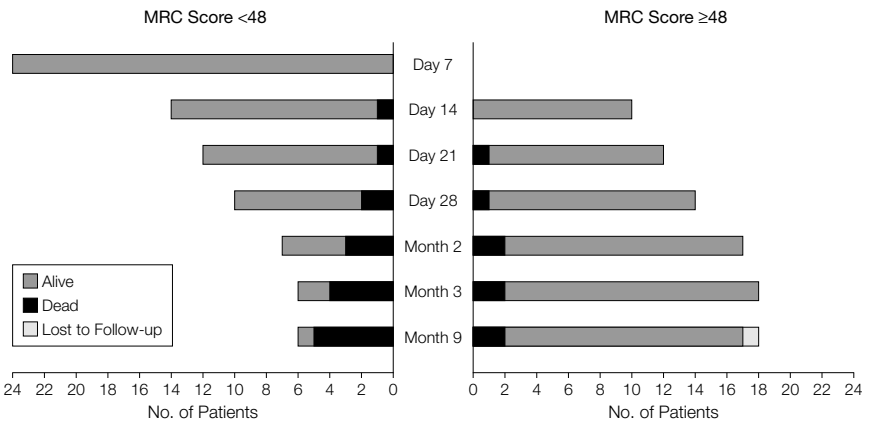
Duration of mechanical ventilation and ICU stay before and after awakening and the total duration of mechanical ventilation and ICU stay. The dotted line shows the first day with an awakening and comprehension score of 3 or more (day 1). Bar graphs on the left of the dotted line show the mean (SD) duration of mechanical ventilation and ICU stay before day 1; bar graphs on the right show the mean (SD) duration of mechanical ventilation and ICU stay after day 1.

The systematic clinical detection of paresis in our study showed that a quarter of ICU patients who had undergone mechanical ventilation for 7 or more days and achieved satisfactory recovery of consciousness had severe motor weakness. This syndrome was characterized by a symmetrical alteration in muscle strength mainly in the proximal regions of the limbs. We found a sensory-motor axonopathy in all of the ICUAP patients. Furthermore, histologic features of primary myopathic change, along with neurogenic abnormalities, were also observed in all patients who still had paresis 1 week after the initial diagnosis. Although early studies[3] considered peripheral neuropathy to be the main mechanism of ICUAP, our findings suggest that both peripheral nerve and muscle are at the origin of ICUAP and that the term *critical illness polyneuropathy* may be too restrictive.

Neuromuscular dysfunction had resolved (MRC score, ≥48) within 3 weeks in half of our patients, and, among the 16 survivors at 9-month follow-up, 15 had recovered an MRC score of 48 or higher and 12 were able to return home. This finding indicates that improvement throughout several weeks or months is the rule for most patients. Although the recently summarized rehabilitation literature on long-term outcome of critical illness neuropathy or myopathy is predominantly based on retrospective case series,[20] our findings are consistent with the few prospective studies[6,8,21] that report follow-up of patients with critical illness polyneuropathy detected by electromyography.

In our study, 4 independent variables were associated with the occurrence of clinical motor weakness. The number of days with dysfunction in at least 2 organs before awakening was significantly higher in ICUAP patients than in the controls, suggesting that the duration, rather than the severity, of multiple-organ dysfunction plays a significant role in ICUAP. Thus, preventive or therapeutic interventions to reduce the risk of multiple-organ dysfunction may also decrease the risk of ICUAP.

Figure 4. Nine-Month Follow-up Data for the 24 Patients With Intensive Care Unit–Acquired Paresis



One patient with severely worsened consciousness from day 10 was considered to have persistent intensive care unit–acquired paresis until death at month 3. MRC indicates Medical Research Council.

We found a strong association between administration of corticosteroids and the occurrence of ICUAP. The deleterious effect of corticosteroids on neuromuscular function in ICU patients has been observed in several cohort studies of patients who received a combination of high doses of corticosteroids and neuromuscular blocking agents to treat severe acute asthma.[19,22] The use of corticosteroids in the general ICU population would logically expose general ICU patients to similar neuromuscular complications. During our study period, one fourth of our patients received corticosteroids at least once, mostly for COPD exacerbation and septic shock. Our study is the first prospective cohort study, to our knowledge, to suggest a deleterious effect of corticosteroids in an unselected population of ICU patients. Non-ICU patients who receive corticosteroids are susceptible to developing histologic features of myopathy that include type 2 fiber atrophy and myosinolysis, which were commonly observed in our ICUAP patients. These lesions are the consequence of corticosteroid muscle receptor stimulation by exogenous corticosteroids[23] and are experimentally enhanced by muscle denervation.[24] Because all of our patients had axonal neuropathy, this may have contributed to the corticosteroid-specific muscle involvement. Interestingly, although corticosteroids were administered before day 1 more frequently in patients with ICUAP compared with those without ICUAP, no significant difference in the duration of administration or the cumulative dosage of corticosteroids was observed between the 2 groups. One explanation may be that the medical condition that prompts corticosteroid administration is indeed responsible for the neuromuscular dysfunction. However, neither COPD exacerbation nor septic shock was an independent predictor of ICUAP. Alternatively, corticosteroids may act as a trigger for neuromuscular dysfunction, which was previously unmasked or further maintained by other deleterious conditions, such as axonal neuropathy. Although we found a significant association between corticosteroids and ICUAP and not necessarily a definite causal relationship, this finding should prompt physicians to carefully weigh the indications of corticosteroids in critically ill patients and restrict their use to conditions such as septic shock, unresolved adult respiratory distress syndrome, and status asthmaticus in which corticosteroids have been shown to have a significant impact on morbidity and mortality.[25-29]

The duration of mechanical ventilation before awakening was also significantly associated with the occurrence of ICUAP and likely reflects the negative effect of immobilization on neuromuscular function, given that increased expression of corticosteroid muscle receptors has been associated with complete immobilization.[30] Our finding raises the question of whether preservation of minimal muscle activity in ICU patients by minimal or interrupted sedation and analgesia or by regular and frequent passive physiotherapy may be beneficial.

Surprisingly, female sex was found to be independently associated with a higher rate of ICUAP in our study. There is no clear explanation for this finding. In our population, only 2 female patients were younger than 50 years. Muscle strength is physiologically lower in women than in men in both upper and lower limbs[31] and in postmenopausal women compared with premenopausal and postmenopausal women receiving hormone replacement therapy.[32] Pharmacokinetic differences between male and female patients might also contribute to this finding.[33]

Although the use of aminoglycosides[21] and the presence of renal failure[9] have been previously associated with electrophysiologic or histologic abnormalities in ICU patients, they were not associated with ICUAP in our study. This may be due to a true lack of independent clinical effect or an insufficient sample size, even though our study was conducted in one of the largest cohorts of patients potentially at risk for ICUAP reported to date. Similarly, no significant difference was found between ICUAP and control patients with and without neuromuscular blockers. This finding does not rule out the possibility of a deleterious effect of specific modes of neuromuscular blocker administration, particularly continuous intravenous infusion. However, we could not compare this factor in our study, since few patients received continuous infusion of neuromuscular blockers (4 in the ICUAP and 2 in the control group). Such a comparison would require widespread use of neuromuscular blockers and a very large study, which may be difficult, given growing awareness of the potentially deleterious effect of neuromuscular blockers on the peripheral nervous system and the restricted conditions that justify their administration.[34]

In our study, ICUAP patients had a significantly longer *total* duration of mechanical ventilation compared with control patients. The duration of mechanical ventilation *after awakening* and establishment of the diagnosis of ICUAP, which might be the most relevant assessment of the impact of ICUAP on the additional mechanical ventilation requirement, was also significantly longer in ICUAP patients than in controls. However, the exact contribution of neuromuscular disorders to delayed weaning from mechanical ventilation and prolonged ICU stay remains to be established through concomitant evaluations of peripheral and respiratory neuromuscular function and electrophysiology and inclusion of ICUAP in future analysis of variables influencing the duration of mechanical ventilation.

Although we studied ICU patients who recovered satisfactory awakening after at least 7 days of mechanical ventilation, ICUAP may also occur in patients who undergo mechanical ventilation for fewer than 7 days. Further research is warranted to determine the generalizability of our results to the overall ICU population of patients who undergo mechanical ventilation.

In summary, the use of simple bedside criteria allowed us to identify a high incidence of ICUAP among ICU patients during the recovery phase of severe critical illness. Patients with ICUAP have combined peripheral nerve and muscle involvement and require prolonged mechanical ventilation. The risk factors identified in our study suggest that preventive measures, including limiting corticosteroid administration to patients with evidence-based indications, may be warranted.

Author Contributions: The principal investigator, Bernard De Jonghe, MD, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: De Jonghe, Sharshar, Lefaucheur, Authier, Durand-Zaleski, Carlet, Raphael, Outin, Bastuji-Garin.
Acquisition of data: De Jonghe, Sharshar, Lefaucheur, Authier, Durand-Zaleski, Boussarsar, Cerf, Renaud, Mesrati, Bastuji-Garin.
Analysis and interpretation of data: De Jonghe, Sharshar, Lefaucheur, Authier, Durand-Zaleski, Boussarsar, Raphael, Bastuji-Garin.
Drafting of the manuscript: De Jonghe, Sharshar, Lefaucheur, Raphael, Bastuji-Garin.
Critical revision of the manuscript for important intellectual content: De Jonghe, Sharshar, Lefaucheur, Authier, Durand-Zaleski, Boussarsar, Cerf, Renaud, Mesrati, Carlet, Raphael, Outin, Bastuji-Garin.
Statistical expertise: Durand-Zaleski, Bastuji-Garin.
Obtained funding: De Jonghe, Sharshar, Lefaucheur.
Study supervision: Carlet, Raphael, Outin.
Funding/Support: This study was funded by a grant from GlaxoSmithKline Laboratory, Marly-Le-Roi, France.
Role of Sponsor: GlaxoSmithKline Laboratory had no role in the design and conduct of the study; in the collection, analysis, and interpretation of the data; and in the preparation, review, or approval of the manuscript.
The Members of the Groupe d'Etude et de Réflexion sur les Neuromyopathies en Reanimation are F. J. Authier, Laboratoire d'Histologie, Créteil, France; S. Bastuji-Garin and I. Durand-Zaleski, Département de Santé Publique, Créteil; J. P. Bedos and G. Troché, Réanimation Polyvalente, Versailles, France; M. Boussarsar, L. Brochard, and N. Kouraichi, Réanimation Médicale, Créteil; J. Carlet and B. Misset, Réanimation Polyvalente, Hôpital Saint-Joseph, Paris, France; C. Cerf and G. D'honneur, Réanimation Chirurgicale, Créteil; B. De Jonghe and H. Outin, Réanimation Médicale, Poissy, France; J. Duranteau, Réanimation Chirurgicale, Kremlin-Bicêtre; J. P. Lefaucheur, F. Mesrati, and M. L. Sublet, Service de Physiologie–Explorations Fonctionnelles, Hôpital Henri Mondor, Créteil; F. Lagneau, Département d'Anesthésie, Clichy, France; A. Mebazaa, D. Payen, and E. Renaud, Réanimation Chirurgicale, Hôpital Lariboisière, Paris; P. Moine, Département d'Anesthésie, Kremlin-Bicêtre, France; B. Plaud, Département d'Anesthésie, Hôpital Rothschild, Paris; J. C. Raphaël and T. Sharshar, Réanimation Médicale, Garches, France; and D. Renon and P. Sandrat, Laboratoire Glaxo Wellcome, Marly-Le-Roi, France.

REFERENCES

1. MacFarlane I, Rosenthal F. Severe myopathy after status asthmaticus. *Lancet*. 1977;2:615.
2. Leijten F, de-Weerd A, Poortvliet D, de-Ridder V, Ulrich C, Harink-de-Weerd J. Critical illness polyneuropathy in multiple organ dysfunction syndrome and weaning from the ventilator. *Intensive Care Med*. 1996; 22:856-861.
3. Bolton C, Gilbert J, Fhahn A, Sibbald W. Polyneuropathy in critically ill patients. *J Neurol Neurosurg Psychiatry*. 1984;47:1223-1231.
4. DeJonghe B, Cook D, Sharshar T, Lefaucheur J, Carlet J, Outin H. Acquired neuromuscular disorders in critically ill patients: a systematic review. *Intensive Care Med*. 1998;24:1242-1250.
5. DeJonghe B, Cook D, Outin H. Risk factors for polyneuromyopathy of critical illness. In: Vincent J, ed. *Yearbook of Intensive Care and Emergency Medicine*. New York, NY: Springer-Verlag; 1999:322-330.
6. Witt N, Zochodne D, Bolton C, et al. Peripheral nerve function in sepsis and multiple organ failure. *Chest*. 1991;99:176-184.

7. Coakley J. Preliminary observations on the neuromuscular abnormalities in patients with organ failure and sepsis. *Intensive Care Med.* 1993;19:323-328.
8. Berek K, Margreiter J, Willeit J, Berek A, Schmutzhard E, Mutz N. Polyneuropathies in critically ill patients: a prospective evaluation. *Intensive Care Med.* 1996;22:849-855.
9. Helliwell TR, Coakley JH, Wagenmakers AJ, et al. Necrotizing myopathy in critically-ill patients. *J Pathol*. 1991;164:307-314.
10. Kleyweg R, VanDerMeché F, Schmitz P. Interobserver agreement in the assessment of muscle strength and functional abilities in Guillain-Barré syndrome. *Muscle Nerve.* 1991;14:1103-1109.
11. Liveson J, Ma D. *Laboratory Reference for Clinical Neurophysiology.* Philadelphia, Pa: FA Davis Co; 1992.
12. Dubowitz V, Sewry C, Fitzsimons R. Definition of pathological changes seen in muscle biopsies. In: Dubowitz V, ed. *Muscle Biopsy: A Practical Approach.* 2nd ed. London, England: Baillière-Tindall; 1985:82-128.
13. Miettinen O. Estimability and estimation in case-referent studies. *Am J Epidemiol*. 1976;103:226-235.
14. LeGall J, Lemeshow S, Saulnier F. A new simplified acute physiologic score (SAPS II) based on a European/North American multicenter study. *JAMA*. 1993;270:2957-2963.
15. Fagon JY, Chastre J, Novara A, Medioni P, Gibert C. Characterization of intensive care unit patients using a model based on the presence or absence of organ dysfunctions and/or infection: the ODIN model. *Intensive Care Med*. 1993;19:137-144.
16. de Letter MA, Schmitz PI, Visser LH, et al. Risk factors for the development of polyneuropathy and myopathy in critically ill patients. *Crit Care Med*. 2001; 29:2281-2286.
17. Campellone JV, Lacomis D, Kramer DJ, Van Cott AC, Giuliani MJ. Acute myopathy after liver transplantation. *Neurology*. 1998;50:46-53.
18. Latronico N, Fenzi F, Recupero D, et al. Critical illness myopathy and neuropathy. *Lancet*. 1996;347: 1579-1582.
19. Douglass J. Myopathy in severe asthma. *Am Rev Respir Dis*. 1992;146:517-519.
20. van der Schaaf M, Beelen A, de Groot IJ. Critical illness polyneuropathy: a summary of the literature on rehabilitation outcome. *Disabil Rehabil*. 2000;22:808-810.
21. Leijten FS, Harinck-de Weerd JE, Poortvliet DC, de-Weerd AW. The role of polyneuropathy in motor convalescence after prolonged mechanical ventilation. *JAMA.* 1995;274:1221-1225.
22. Leatherman JW, Fluegel WL, David WS, Davies SF, Iber C. Muscle weakness in mechanically ventilated patients with severe asthma. *Am J Respir Crit Care Med.* 1996;153:1686-1690.
23. Konagaya M, Bernard PA, Max SR. Blockade of glucocorticoid receptor binding and inhibition of dexamethasone-induced muscle atrophy in the rat by RU38486, a potent glucocorticoid antagonist. *Endocrinology*. 1986;119:375-380.
24. Du Bois DC, Almon RR. A possible role for glucocorticoids in denervation atrophy. *Muscle Nerve*. 1981;4:370-373.
25. Bollaert PE, Charpentier C, Levy B, Debouverie M, Audibert G, Larcan A. Reversal of late septic shock with supraphysiologic doses of hydrocortisone. *Crit Care Med*. 1998;26:645-650.
26. Briegel J, Forst H, Haller M, et al. Stress doses of hydrocortisone reverse hyperdynamic septic shock: a prospective, randomized, double-blind, single-center study. *Crit Care Med.* 1999;27:723-732.
27. Annane D, Sebille V, Charpentier C, et al. Effect of treatment with low doses of hydrocortisone and fludrocortisone on mortality in patients with septic shock. *JAMA.* 2002;288:862-871.
28. Meduri GU, Headley AS, Golden E, et al. Effect of prolonged methylprednisolone therapy in unresolving acute respiratory distress syndrome: a randomized controlled trial. *JAMA*. 1998;280:159-165.
29. Levy BD, Kitch B, Fanta CH. Medical and ventilatory management of status asthmaticus. *Intensive Care Med*. 1998;24:105-117.
30. Du Bois DC, Almon RR. Disuse atrophy of skeletal muscle is associated with an increase in number of glucocorticoid receptors. *Endocrinology*. 1980;107: 1649-1651.
31. Miller AE, MacDougall JD, Tarnopolsky MA, Sale DG. Gender differences in strength and muscle fiber characteristics. *Eur J Appl Physiol Occup Physiol*. 1993; 66:254-262.
32. Phillips SK, Rook KM, Siddle NC, Bruce SA, Woledge RC. Muscle weakness in women occurs at an earlier age than in men, but strength is preserved by hormone replacement therapy. *Clin Sci (Colch).* 1993;84:95-98.
33. Xue F, An G, Liao X, Zou Q, Luo L. The pharmacokinetics of vecuronium in male and female patients. *Anesth Analg.* 1998;86:1322-1327.
34. Murray MJ, Cowen J, DeBlock H, et al. Clinical practice guidelines for sustained neuromuscular blockade in the adult critically ill patient. *Crit Care Med.* 2002;30:142-156.

Every idea is a source of life and light which illuminates the words, facts, examples, and emotions that are dead—or deadly—and dark without them.
—Mortimer J. Adler (1902-2001)