Brainstem responses can predict death and delirium in sedated patients in intensive care unit*

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Objectives: **In critically ill patients, the assessment of neurologic function can be difficult because of the use of sedative agents. It is not known whether neurologic signs observed under sedation can predict short-term outcomes. The objective of this study was to assess whether abnormal brainstem responses within the first 24 hrs of sedation are associated with mortality and altered mental status postsedation.**

Design: **Observational prospective study including an initial single-center and a subsequent multicenter study to develop and then validate the prognostic models.**

Setting: **Three mixed and two medical intensive care units.**

Patients: **Mechanically ventilated intensive care unit patients sedated with midazolam (± sufentanyl).**

Interventions: **Neurologic examination including the Glasgow Coma Scale, the Assessment to Intensive Care Environment score, cranial nerve examination, response to noxious stimuli, and the cough reflex was performed.**

Measurements and Main Results: **Seventy-two patients were included in the initial group and 72 in a subsequent validation study. Neurologic responses were independent of sedative dose. Twenty-two patients in the development cohort and 21 (29%) in the validation group died within 28 days of inclusion. Adjusted for Simplified Acute Physiology Score II score, absent cough reflex was independently associated with 28-day mortality in the development (adjusted odds ratio [OR], 7.80; 95% confidence interval [CI], 2.00–30.4; $p = .003$) and validation groups (adjusted OR, 5.44; 95% CI, 1.35–22.0; $p = .017$). Absent oculocephalic response, adjusted for Simplified Acute Physiology Score II score, was independently associated with altered mental status after the withdrawal of sedation in the development (adjusted OR, 4.54; 95% CI, 1.34–15.4; $p = .015$) and validation groups (adjusted OR, 6.10; 95% CI, 1.18–25.5; $p = .012$).**

Conclusions: **Assessment of brainstem responses is feasible in sedated critically ill patients and loss of selected responses is predictive of mortality and altered mental status. (Crit Care Med 2011; 39:1960–1967)**

KEY WORDS: sedation; brainstem reflex; septic shock; neurological assessment; delirium

Sedation is required in some critically ill patients for reasons of safety or comfort. It has been clearly shown that either titration or daily interruption of sedation can significantly reduce the length of mechanical ventilation and intensive care unit (ICU) stay (1–5). However, even with this approach, sedation is required for a median of between 2 (6) and 4 (7) days and in one trial sedation was required in 20% of critically ill patients assigned to no sedation (8).

Brain dysfunction is a major determinant of severity of critical illness but sedation is thought to limit its assessment. It remains unknown how sedation affects neurologic responses that can be tested in comatose patients. Neurologic responses might have prognostic implications for sedated patients (9–11), especially brainstem reflexes, because the brainstem controls various vital functions.

The brainstem is also involved in arousal and consciousness. A significant proportion of patients in the ICU may develop coma, confusion, or delirium (7, 12–15). Predicting the occurrence of altered mental status in critically ill patients is a crucial issue, because acute brain dysfunction has been associated with increased mortality and morbidity (12, 13, 16). We wanted to establish if it is possible to make such predictions even with the confounding influence of sedation. We hypothesized that assessment of brainstem reflexes under sedation could

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help to identify patients who will be at increased risk of death or altered mental status while in the ICU.

PATIENTS AND METHODS

Population

The study population consisted of two sets of adult patients, i.e., a development and a validation set. One mixed ICU (Raymond Poincaré Teaching Hospital) participated in the development study from June 2004 to December 2005 and five (three mixed and two medical ICUs) in the validation study from December 2007 to June 2009.

For both sets, patients were eligible if they were mechanically ventilated and had been sedated with midazolam with or without sufentanil for at least 12 hrs. They were excluded if they had received neuromuscular-blocking agents (other than for intubation), had a peripheral neurologic disorder involving the cranial nerves (i.e., Guillain-Barré syndrome and myasthenia gravis), or had been referred to ICU for a stroke, central nervous system infection, or a head injury. Patients with quadriplegia or paraplegia resulting from spinal cord injury were not excluded. The study was approved by the ethics committee of Saint-Germain en Laye.

Sedation

Sedatives and analgesics were all administered by continuous infusion, and the infusion rates and cumulative doses of midazolam (milligrams, milligrams/kilogram) and sufentanil (micrograms, micrograms/kilogram) were recorded at the time of assessment. Management of sedation differed between the development and validation sets. In the former, the physician in charge of the patient adjusted the dosage of sedative and analgesics drugs without a formal protocol. In the latter, they either interrupted the sedation daily (three centers) or titrated it (two centers) according to the Richmond Agitation Sedation Scale (RASS) (5). Discontinuation was decided every morning. Titration was performed twice a day and target RASS level depended on each center's practice and severity of the patients (4).

Neurologic Examination

This involved 1) assessment of level of consciousness using the motor and eye responses of the Glasgow Coma Scale; 2) assessment of sedation level using the Adaptation to the Intensive Care Environment (ATICE) scale (4) and RASS (only for the validation set); and 3) cranial nerve examination, which included resting eye position (normal or abnormal), spontaneous eye movement (present or absent), pupil size (miosis, normal, or mydriasis) and response to light, blink response to strong light, corneal reflexes, grimacing in response to retromandibular pressure, oculocephalic response to lateral passive head rotation, and cough response after tracheal suctioning. The ATICE scale was in routine use in one center and the RASS in others. However, all investigators were experienced in using both scores.

Neurologic examination was initially performed between the 12th and the 24th hours of continuous sedation (day 1) and then daily after morning rounds until the patient regained wakefulness as defined by eyes opening to verbal order according to the ATICE scale.

For the development set, all examinations were performed by a senior neurologist (T.S.). For the validation set, all examinations were performed by either a senior neurologist (B.R, C.G., and R.S) or by a senior ICU physician (S.S, E.I, J.A., and S.G.) trained by a senior neurologist (T.S.). Investigators in the validation study were not aware of the results of the development study. The physician in charge of the patient was not informed of the results of the neurologic examination unless they were suggestive of a focal brain lesion.

Assessment of Altered Mental Status

For 3 days after discontinuation of sedation, neurologic evaluation was performed daily to evaluate mental status. Altered mental status was considered to be present if the patient remained comatose at least 3 days after discontinuation of sedation or developed confusion or delirium within the 3 days after discontinuation of sedation. Because alteration of consciousness was assessed differently in the development and validation cohort, we have used two different terms for this phenomenon, i.e., confusion and delirium. In the development set, confusion was assessed with the help of the ATICE scale, which grades awakeness, comprehension, calmness, patient-ventilator synchrony, and facial relaxation (4). Confusion was considered to be present when awakening was graded at least four (eyes opening to verbal order or spontaneously) and comprehension <4 or agitation <2. Comprehension <4 indicates that the patient is able to perform at most three of the following tasks: 1) open or close eyes to command; 2) open your mouth; 3) look at me; 4) nod yes with your head; and 5) close your eyes and open your mouth. Agitation <2 indicates that agitation is either life-threatening or not calmed by verbal order (4). In the validation set, delirium was assessed by a separate investigator unaware of the preceding neurologic examinations using the Confusion Assessment Method for the Intensive Care Unit score, as described elsewhere (12, 13).

Clinical Data. Demographic characteristics, category of admission (medical or surgical), comorbidities, pre-existing risk factors for delirium (17), and ICU admission diagnosis were recorded. The Simplified Acute Physiology Score II was assessed at admission (18) and the Sequential Organ Failure Assessment score daily until recovery of wakefulness (19). Cumulative doses of midazolam and subfentanyl between onset and discontinuation were recorded. At the time of each neurologic examination, vital signs, hematologic and biochemical parameters, and drugs were recorded.

Statistical Analyses

Association of day 1 neurologic responses, sedative doses, Simplified Acute Physiology Score II, ATICE, and Glasgow Coma Scale scores with 28-day mortality and altered mental status was analyzed in the development set as described subsequently. The final models derived were then fitted in the validation set. Marginal association was tested using Fisher's exact test for binary variables and Wilcoxon test for continuous variables. Variables independently associated with each of the outcomes were determined using multiple logistic regression with a backward stepwise variable selection procedure using modified Akaike criterion to remove nonsignificant variables (20). It was decided that all models would be adjusted for Simplified Acute Physiology Score II at admission irrespective of the model selection procedure. The collinearity between considered factors was assessed using Pearson's correlation coefficient and Somers' Dxy rank correlation if predictors were not both continuous. The validity of the models was checked using generalized additive models with splines and le Cessie and van Houwelingen goodness-of-fit test (21). Interactions between the selected factors were then tested. The predictive value of the whole model was expressed in terms of C-index. The evolution of RASS and drug doses during the first 4 days after inclusion was analyzed using mixed effects regression models with random intercept and slopes per subject. All tests were two-sided, and a p value of .05 was considered to be significant. Analyses were performed using R 2.2.1 (The R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

One hundred forty-four patients were enrolled, 72 in each set (Fig. 1). Patients of the validation set were older and had more severe critical illness (Table 1). Criteria for intubation and sedation did not differ between development and validation sets (Table 1). In the validation group, daily interruption and titration of sedation were performed in 40 (56%) and 32 (44%) patients, respectively. These procedures were associated with an increase in RASS level and a reduction in midazolam and sufentanil infusion rate

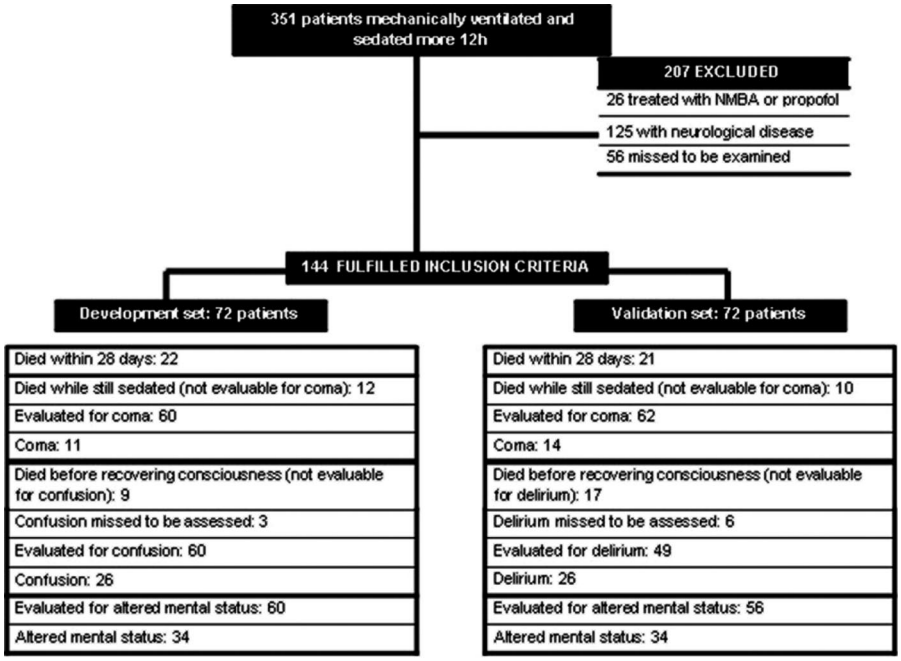

Figure 1. Flow chart. The number of patients included in each center varied from six to 29 and the duration of participation of each center from 1 to 9 mos. Altered mental status was defined as a coma persisting at least 3 days after discontinuation of sedation or occurrence of confusion or delirium within the 3 days after discontinuation of sedation. Confusion was assessed in the development set with the help of the Adaptation to the Intensive Care Environment scale and delirium in the validation set with help of Confusion Assessment Method for the Intensive Care Unit. *NMBA*, neuromuscular-blocking agent.

(Fig. 2). Median duration of sedation was 2 days less in the validation group than in the development one (Table 1).

Neurologic Responses at Day 1. Miosis was less frequent and both grimacing and cough reflex more common in the validation group (Table 2). The cumulative dose of midazolam (milligrams/kilogram) before inclusion was not different between patients with and without any brainstem reflex. Cumulative fentanyl dose (micrograms/kilogram) correlated with miosis and absent blinking. Patients did not differ according to type of admission (medical [73.6%] or surgical [26.4%]) in terms of neurologic presentation or cumulative dose of sedatives.

Neurologic Responses and Mortality. Forty-three (30%) patients died within 28 days of inclusion, including 22 (31%) and 21 (29%) in the development and validation groups, respectively (Table 1). Withdrawal of care after failure of maximal treatment occurred in eight patients and in three patients a ceiling of care was established because of chronic respiratory insufficiency or malignancy.

Cough reflex was more frequently absent at day 1 in patients who died within 28 days in both groups (Table 3). Simplified Acute Physiology Score II and absent cough reflex at day 1 were the independent factors most strongly associated with 28-day mortality in both development and validation sets (Table 4). The mortality rate was higher in patients with absent cough reflex noted at any time during the study: development (17% vs. 41%), validation (17% vs. 63%) and pooled groups (22% vs. 48%; $p = .004$). The predictive model was not affected by type of admission ($p = .70$).

Neurologic Responses and Altered Mental Status. The prevalence of confusion and delirium was 43% and 53% in the development and validation group, respectively (Fig. 1; Table 1). Coma occurred in 11 (18%) patients of the development group and in 14 (23%) of the validation group. Prevalence of altered mental status was 57% and 61% in the development and validation groups, respectively. Among the 25 comatose patients, 17 awoke after the third day of sedation discontinuation. Flumazenil test was performed in five of these 17 patients and was positive. In the eight patients who remained comatose, coma was ascribed to hepatic encephalopathy (n = 3) and to brain lesions (n = 5) complicating severe septic shock or cardiorespiratory arrest secondary to an accidental extubation.

Absence of oculocephalic response at day 1 was more frequent in patients who subsequently developed altered mental status irrespective of criteria used (Table 5). In the validation set, altered mental status was more common in medical than surgical patients. Absent oculocephalic response at day 1 remained the best independent factor associated with altered mental status in both sets after adjustment for Simplified Acute Physiology Score II or medical admission (Table 6). Altered mental status occurred more frequently in patients without than in patients with an oculocephalic response observed at any time in development (42% vs. 67%), validation (43 vs. 73%), and pooled groups (43% vs. 71%, $p = .004$). Pre-existing risk factors for delirium (notably cognitive alteration) and presence of altered mental status before sedation were not associated with absent oculocephalic response or occurrence of altered mental status after discontinuation of sedation. There was a trend to quicker increase in RASS after the first day of sedation in patients with than without oculocephalic response at inclusion ($p = .07$). The predictive model was affected not by sedation procedure ($p = .29$) or center ($p = .47$) or type of admission ($p = .36$).

DISCUSSION

This study shows that in mechanically ventilated ICU patients assessed while under sedation, the absence of cough reflex is independently associated with 28-day mortality and that the absence of the oculocephalic response is independently associated with the occurrence of altered mental status (i.e., coma, confusion, or delirium) within the 3 days after discontinuation of sedation. These results indicate that neurologic examination yields useful prognostic information in sedated ICU patients. They also point out the pathogenic role of early brainstem dysfunction in critical illness.

A possible neuroanatomic explanation exists for these findings. The tracheal suction-triggered cough reflex is controlled by the medullary cough center (9). The oculocephalic response involves the vestibular nuclei and the parapontine reticular formation as well as the medial longitudinal fasciculus, which connects the abducens nucleus with the opposite oculomotor nucleus (9). Thus, the cough pathway is in the vicinity of cardiovascular and respiratory centers. The oculoce-

Table 1. Characteristics of the patients at inclusion

	Development Set (n = 72)	Validation Set (n = 72)
Women, %	24 (33)	28 (39)
Age, yrs[a]	58 (46–74)	69 (51–80)
Surgical admission (%)	16 (22)	22 (31)
Simplified Acute Physiology Score II at admission	50 (37–61)	57 (45–67)
Pre-existing risk factor for delirium	37 (52)	45 (63)
Pre-existing cognitive alteration	7 (10)	9 (13)
ICU admission diagnosis		
Acute respiratory distress syndrome	26 (36)	9 (13)
Sepsis	50 (69)	45 (63)
Septic shock	26 (36)	17 (24)
Hemorrhagic shock	2 (3)	2 (3)
Cardiogenic shock	4 (6)	2 (3)
Acute exacerbation of chronic obstructive pulmonary disease	8 (11)	3 (4)
Outcome		
Duration of sedation, days[a]	5 (2–8)	3 (2–6)
Confusion/delirium at awakening (%)	26 (43)[b]	26 (53)[c]
Coma (%)	11 (18)[d]	14 (23)[e]
Altered mental status (%)	34 (57)[f]	34 (61)[g]
Mortality rate at day 28 (%)	22 (31)	21 (29)
Delay between inclusion and death, days	11 (2–15)	4 (3–19)
Mortality rate in ICU (%)	26 (36)	27 (38)
Length of stay in ICU, days	18 (9 to 33)	15 (9 to 25)
SOFA[a]	4 (2–6)	10 (8–13)
SOFA renal	1 (0–3)	1 (0–2)
SOFA liver	0 (0–0)	0 (0–1)
Systolic arterial pressure, mm Hg[a]	126 (108–143)	112 (101–124)
Heart rate, beats/min	96 (84–114)	100 (82–118)
$Paco_2$, kPa	5.8 (5.0–6.9)	5.5 (4.7–6.3)
PaO_2, kPa	14 (11–19)	14 (11–17)
Plasma sodium level, mmol/L	138 (135–141)	140 (137–142)
Plasma creatinine level, mmol/L	114 (73–193)	117 (67–141)
Plasma bilirubin level, μmol/L	10 (6–19)	9 (6–19)
Plasma glucose level, mmol/L	7.7 (6.1–11.0)	7.7 (6.1–10.9)
Criteria for intubation		
Acute respiratory failure	34 (47)	32 (44)
Coma	18 (25)	3 (4)
Shock	16 (22)	29 (40)
Surgery	10 (14)	6 (8)
Cardiorespiratory arrest	4 (6)	0 (0)
Criteria for sedation		
Synchrony with the ventilator	51 (71)	55 (76)
Agitation	27 (38)	14 (19)
Analgesia	7 (10)	12 (17)

ICU, intensive care unit; SOFA, Sequential Organ Failure Assessment.

[a]Difference statistically significant between the two groups ($p < .05$); [b]confusion evaluated in 60 patients with Adaptation to the Intensive Care Environment score; [c]delirium evaluated in 49 patients with Confusion Assessment Method for the Intensive Care Unit; [d,e]coma evaluated in 60 and 62 patients, respectively; [f,g]altered mental status evaluated in 60 and 56 patients, respectively. Data are presented as median (interquartile range) or frequency (percent).

phalic pathway is in proximity to the ascending reticular activating system, which controls arousal. It is therefore conceivable that abolition of cough reflex is a surrogate marker for dysfunction of the respiratory and cardiovascular centers (22–24). Similarly, absence of oculocephalic response might reflect impairment of the ascending reticular activating system that results in delirium after discontinuation of sedation. The fact that increase in RASS tended to be higher in patients with an intact oculocephalic response, whereas RASS at inclusion and sedation procedure did not differ between these two groups is consistent with this hypothesis. Interestingly, autonomic centers and ascending reticular activating system are liable to functional or structural damage during critical illness (22–25). Furthermore, dysfunction of the locus coeruleus, a nucleus of the ascending reticular activating system, may be involved in sepsis-related delirium (26). It is impossible to determine whether cough reflex and oculocephalic responses are abolished because of sedation (even if not in dose-dependent way) because of other factors related to critical illness or both. It could be that during critical illness, neurons become more sensitive to sedation or that sedation makes neurons more vulnerable to insulting factors released during critical illness (25, 27).

In contrast to the development set, sedation was either titrated or interrupted daily in the validation group. Sedation was not standardized in all participating centers, because this would have implied changing this observational study into an intervention one with each center modifying its procedures. At the time of study design, there was no evidence that daily discontinuation reduced the occurrence of delirium more than titration and these two approaches have yet to be compared in this way. Interestingly, studies have found that delirium affected >70% of patients assigned to daily midazolam discontinuation (6) or titration on RASS (7). Finally, specifying one strategy could have raised the issue that our findings are not extendable to another procedure. In the validation group, the procedures adopted led to a 2-day reduction in duration of sedation compared with the development group as well as a reduction each day in the dose of midazolam and an increase each day in RASS level. Our results are comparable to those reported in clinical trials on daily interruption or titration (2, 6). Sedation management did not appear to be a confounding factor because the predictive model for altered mental status was not affected by the participating center or the use of daily discontinuation or titration procedures. This suggests that modalities and effect of sedation within the 24 first hours have an impact on outcome and may need to be changed. This hypothesis does not of course conflict with the finding that sedation can have a detrimental effect beyond the first 24 hrs as well. Various studies have shown that alteration of mental status increases with duration and cumulative dose of sedatives, notably benzodiazepines, even when an earlier light sedation is targeted (6, 7, 12–15). Delirium will develop in a given individual dependent on their individual susceptibility to sedatives but also on multiple factors, including pre-existing and environmental factors as well as the cause and severity of critical illness.

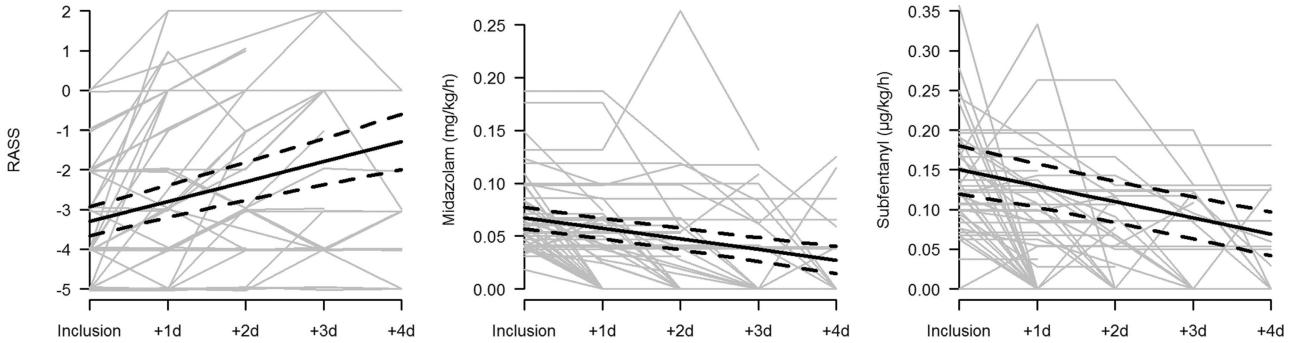

Figure 2. *Left panel*, Individual and overall change in Richmond Agitation Sedation Scale (*RASS*) within the 4 days after inclusion. *Central panel*, Individual and overall change in midazolam infusion rate (mg/kg/hr) within the 4 days after inclusion. *Right panel*, Individual and overall change in subfentanyl infusion rate (µg/kg/hr) within the 4 days after inclusion.

Table 2. Neurologic responses at inclusion

	Development Set	Validation Set
Number of patients	72	72
Altered mental status before sedation	35 (49)	39 (54)
Midazolam, mg/kg/hr	0.07 (0.05–0.11)	0.06 (0.05–0.09)
Cumulative dose of midazolam, mg/kg	0.9 (0.6–1.8)	1.3 (0.8–2.0)
Subfentanyl, µg/kg/hr	0.2 (0.1–0.3)	0.1 (0.1–0.2)
Cumulative dose of subfentanyl, µg/kg	2.0. (0.8–4.0)	2.0 (0.7–4.6)
Midazolam and fentanyl (%)	61 (85)	61 (85)
Time from onset of sedation to inclusion, hrs	12 (12–24)	12 (12–24)
Assessment to Intensive Care Environment (from 0 to 20)	9 (9–10)	9 (9–10)
Awakeness (from 0 to 5)	0 (0–1)	1 (0–2)
Comprehension (from 0 to 5)	0 (0–0)	0 (0–0)
Calmness (from 0 to 3)	3 (3–3)	3 (3–3)
Ventilator synchrony (from 0 to 4)	3 (3–3)	3 (3–4)
Face relaxation (from 0 to 3)	3 (3–3)	3 (2–3)
Glasgow Coma Scale (from 3 to 15)	3 (3–4)	3 (3–7)
Eyes response (from 1 to 4)	1 (1–1)	1 (1–2)
Motor response (from 1 to 6)	1 (1–1)	1 (1–4)
Richmond Assessment Sedation Scale	Not tested	− 4 (− 4 to − 2)
Absent patellar reflex (%)	27 (39)	29 (41)
Absent biceps reflex (%)	30 (42)	28 (39)
Plantar reflex (%)	7 (10)	8 (11)
Blinking to strong light (%)	31 (43)	28 (39)
Absent eye movement (%)	66 (93)	67 (93)
Myosis (%)	45 (63)	38 (54)
Pupillary light response (%)	51 (71)	58 (82)
Corneal reflex (%)	65 (90)	66 (92)
Oculocephalic response (%)	32 (47)	33 (46)
Cough response (%)	36 (51)	60 (83)
Grimacing (%)	41 (57)	48 (69)

Data are presented as median (interquartile range) or frequency (percent).

It is established that both benzodiazepines and opioid agents can alter brainstem functions, including cough reflex, pain, and vestibular responses (28–30). We found that, in critically ill patients, brainstem reflexes do not directly depend on the infusion rate or cumulative doses of midazolam or sufentanil. It is plausible that, for the range of doses used in our patients, such relationships could not be evidenced, but also that infusion rate and cumulative dose did not reflect brain concentrations of drug. Only patients sedated with midazolam were enrolled to obtain a pharmacologically homogeneous group. Midazolam is still commonly used for sedation in the ICU (31), although the use of propofol is increasing (32) and that of dexmetedetomidine is promising (7, 15). It is possible that the neurologic effects of propofol and midazolam differ, although both drugs potentiate γ-aminobutyrate receptors. It would be of interest to determine whether oculocephalic response is more preserved in patients treated with dexmedetomidine, which acts differently on ascending reticular activating system (26), and the use of which has been found to be less frequently complicated by delirium (7, 15).

The definition of altered mental status in our study needs to be addressed. We assessed confusion using the ATICE in the development group and delirium with the Confusion Assessment Method for the Intensive Care Unit in the validation group. Comprehension and calmness domains of the ATICE enabled us to assess two main features of confusion, i.e., inattention and agitation. The reproducibility of the ATICE is established (4). More importantly, validity of ATICE and of its "comprehension" and "calmness" domains have been confirmed by comparisons with Ramsay scale, Riker scale, Glasgow Coma Scale, and Comfort scale (4). Inattention is the mandatory symptom of delirium, according to the Confusion Assessment Method for the Intensive Care Unit (12, 13). In our validation group, only three patients with confusion according to ATICE had no delirium according to Confusion Assessment Method for the Intensive Care Unit. One can infer from this that almost all patients of the development group in whom confusion was detected had delirium. Furthermore, the prevalence of confusion in the development set and delirium in the validation set were comparable, suggesting that the ATICE criteria used were relevant, although this does not mean that the ATICE score can be adopted as a tool for detecting delirium. Finally, we think that the finding of a relationship between oculocephalic response and altered mental status is strengthened by the fact that it was obtained with two different definitions and with different procedures for sedation management.

In conclusion, this study shows that early assessment of brainstem reflexes

Table 3. Univariate analysis of neurologic responses at day 1 with 28-day mortality

	Development Set		Validation Set
Mortality rate at day 28 (%)	22 (31)		21 (29)
	Odds Ratio (95% Confidence Interval)	*p*	Odds Ratio (95% Confidence Interval)
Simplified Acute Physiology Score II at inclusion	1.05 (1.02–1.08)	.0008	1.04 (1.01–1.07)
Cumulative dose of midazolam per mg/kg	0.99 (0.84–1.16)	.31	0.82 (0.54–1.23)
Cumulative dose of subfentanyl per μg/kg	1.00 (0.96–1.05)	.46	0.74 (0.55–1.00)
Assessment to Intensive Care Environment ≤9	5.15 (1.08–54.7)	.040	1.19 (0.43–3.30)
Glasgow Coma Scale <4	6.67 (1.40–31.7)	.017	7.30 (1.91–27.9)
Richmond Assessment Sedation Scale <−3	Not tested	—	4.93 (1.29–18.8)
Blinking to strong light	0.67 (0.24–1.88)	.61	0.38 (0.12–1.20)
Absent eye movement	0.61 (0.09–3.92)	.63	0.24 (0.04–1.59)
Myosis	1.07 (0.38–3.03)	>.99	0.82 (0.29–2.31)
Absent pupillary light response	2.19 (0.75–6.39)	.17	1.79 (0.51–6.33)
Absent corneal reflex	7.06 (1.25–39.8)	.025	2.67 (0.49–14.4)
Absent oculocephalic response	2.27 (0.78–6.65)	.19	0.94 (0.34–2.60)
Absent cough response	7.56 (2.20–25.9)	.0007	7.23 (1.88–27.8)
Absent grimacing	3.40 (1.19–9.68)	.023	2.80 (0.96–8.22)

Data are presented as odds ratio (95% confidence interval), odds ratio (95% confidence interval).

Table 4. Adjusted analysis for 28-day mortality and altered mental status

	Development Set		Validation Set	
	Odds Ratio (95% Confidence Interval)	*p*	Odds Ratio (95% Confidence Interval)	*p*
Simplified Acute Physiologic Score II at inclusion	1.06 (1.02–1.09)	.003	1.03 (1.00–1.07)	.051
Absent cough response	7.80 (2.00–30.4)	.003	5.44 (1.35–22.0)	.017
C-index (SE)	0.836 (0.055)		0.743 (0.067)	

Data are presented as adjusted odds ratio (95% confidence interval). The model for 28-day mortality was maintained irrespective of the participating center ($p = .62$).

Table 5. Univariate analysis of neurologic responses at day 1 with altered mental status (including confusion/delirium or coma)

	Development Set		Validation Set
Criteria	Confusion or Coma		Delirium or Coma
Events	34/60 (57%)		34/55 (62%)
	Odds Ratio (95% Confidence Interval)	*p*	Odds Ratio (95% Confidence Interval)
Age ≥60 yrs	1.42 (0.50–4.02)	.51	1.21 (0.40–3.67)
Mean dose of midazolam per mg/kg/day	0.79 (0.41–1.53)	.49	1.54 (0.68–3.50)
Mean dose of subfentanyl per μg/kg/day	0.99 (0.72–1.05)	.97	0.88 (0.67–1.15)
Duration of sedation per day	0.79 (0.90–1.06)	.52	0.99 (0.88–1.11)
Medical admission	1.40 (0.39–4.98)	.60	7.58 (2.18–6.37)
Simplified Acute Physiologic Score II at inclusion per unit	1.04 (1.01–1.08)	.014	1.03 (0.99–1.07)
Sepsis at inclusion	1.15 (0.40–3.30)	.80	1.21 (0.33–4.44)
Risk factors for delirium[a]	Not tested		1.93 (0.56–6.60)
Assessment to Intensive Care Environment at inclusion ≤9	5.80 (1.71–19.7)	.005	1.02 (0.34–3.04)
Glasgow Coma Scale at inclusion <4	2.06 (0.71–5.98)	.19	1.90 (0.63–5.73)
Richmond Assessment Sedation Scale	Not tested	—	0.88 (0.29–2.68)
Blinking to strong light	0.60 (0.21–1.68)	.33	2.00 (0.65–6.19)
Myosis	2.40 (0.83–6.97)	.11	1.02 (0.34–3.04)
Absent pupillary light response	3.67 (0.90–14.9)	.069	2.92 (0.56–15.4)
Absent oculocephalic response	5.00 (1.55–16.1)	.007	5.75 (1.73–19.2)
Absent cough response	1.42 (0.50–4.02)	.51	1.64 (0.29–9.32)
Absent grimacing	4.89 (1.39–17.2)	.014	1.56 (0.41–5.89)

[a]Include hypertension, alcohol, tobacco, dementia, and psychiatric disorder.

Data are presented as odds ratio (95% confidence interval).

Table 6. Adjusted analysis for altered mental status

Criteria	Development Set Confusion or Coma		Validation Set Delirium or Coma	
	Odds Ratio (95% Confidence Interval)	*p*	Odds Ratio (95% Confidence Interval)	*p*
Simplified Acute Physiologic Score II at inclusion	1.04 (1.00–1.07)	.058	1.03 (0.99–1.08)	.10
Absent oculocephalic response	4.49 (1.34–15.1)	.015	5.64 (1.63–19.5)	.006
Simplified Acute Physiologic Score II at inclusion	1.04 (1.00–1.07)	.057	1.04 (0.99–1.09)	.088
Medical admission	0.92 (0.21–4.10)	.91	8.26 (1.94–35.2)	.004
Absent oculocephalic response	4.54 (1.34–15.4)	.015	6.10 (1.48–25.1)	.012

Data are presented as adjusted odds ratio (95% confidence interval). The model for altered mental status was maintained, irrespective of the participating center ($p = .47$).

may be useful for estimating the severity of critical illness. It suggests that sedation practices that preserve the oculocephalic response might reduce risk of delirium. Such a practice could be complementary to the titration or daily interruption of sedation. At a more general level, the present findings also emphasize that in the ICU, where there is an increasing tendency to rely on technology, clinical examination still has an important part to play. However, these results need to be confirmed in a larger cohort and with ICU physicians or nurses as observers.

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