Brain Dysfunction

Another Burden for the Chronically Critically Ill

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**Background:** Chronic critical illness is a devastating syndrome of prolonged respiratory failure and other derangements. To our knowledge, no previous research has addressed brain dysfunction in the chronically critically ill, although this topic is important for medical decision making.

**Methods:** We studied a prospective cohort of 203 consecutive, chronically critically ill adults transferred to our hospital’s respiratory care unit (RCU) after tracheotomy for failure to wean. We measured prevalence and duration of coma and delirium during RCU treatment using the Confusion Assessment Method for the Intensive Care Unit with the Richmond Agitation-Sedation Scale. To assess survivors (at 3 and 6 months after RCU discharge), we used a validated telephone Confusion Assessment Method.

**Results:** Before hospitalization, most (153 [75.4%]) of the 203 patients in the study were at home, completely independent (115 [56.7%]), and cognitively intact (116 [82.0%]). In the RCU, 61 (30.0%) were comatose throughout the stay. Approximately half of patients (66 of 142) who were not in coma were delirious. Patients spent an average of 17.9 days (range, 1-153 days) in coma or delirium (average RCU stay, 25.6 days). Half of survivors (79 of 160) had one of these disturbances at RCU discharge. At 6 months, three fourths (151) of the study patients were dead or institutionalized; of 85 survivors, 58 (68.2%) were too profoundly impaired to respond to telephone cognitive assessment, and 53 (62.4%) were dependent in all activities of daily living.

**Conclusions:** Severe, prolonged, and permanent brain dysfunction is a prominent feature of chronic critical illness. These data, together with previous reports of symptom distress and rates of mortality and institutionalization, describe burdens for chronically critically ill patients receiving continued life-prolonging treatment and for their families.

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with acute critical illness, delirium is common,15 has a mean duration of 2.4 ICU days,13 and is associated with higher hospital mortality and morbidity.16 Yet, to our knowledge, no prior research has addressed cognitive disturbance in the context of chronic critical illness. To expand knowledge and enhance decision making, we undertook this study describing the prevalence and duration of brain dysfunction (coma and delirium) among hospitalized, chronically critically ill patients requiring prolonged mechanical ventilation and other treatments.

**METHODS**

**RESPIRATORY CARE UNIT**

We conducted a prospective study in the respiratory care unit (RCU) of our 1100-bed, university-affiliated, urban tertiary referral hospital. The RCU is a 14-bed, in-patient unit for chronically critically ill patients from the hospital’s 5 adult ICUs (medical, surgical, cardiothoracic surgical, cardiac, and neurosurgical); it is analogous to the increasing numbers of long-term acute care facilities across the country. Patients are accepted if they no longer need acute ICU care, are mechanically ventilated via tracheotomy, and, in the clinical opinion of the referring ICU physician, are likely to be liberated from the ventilator. Other chronically critically ill patients may not be transferred to the RCU either because of death in the ICU after tracheotomy or because the tracheotomy was placed in preparation for permanent ventilator support, with no expectation that the patient would ever wean. (From 2001 to 2005, when 335 patients were treated in the RCU, 511 patients underwent tracheotomy and were not admitted to the RCU; of the latter group, 230 [43%] died in the hospital.)

As supervised by pulmonary and critical care physicians with nurse practitioners, RCU treatment is standardized by a detailed health care map and weaning protocol,17 but regular care during the study did not include a protocol for sedation or cognitive assessment. Surviving patients are discharged from the RCU on successful liberation from the ventilator or a clinical determination that further efforts to achieve ventilator independence will not succeed.

**PATIENT ENROLLMENT**

From September 2003 to January 2005, we conducted daily screening to identify eligible patients among all new RCU admissions. We defined eligibility by elective tracheotomy for ICU weaning failure.2,18 Tracheotomy under these circumstances reflects the clinical impression that the patient is expected neither to wean nor to die in the immediate future and therefore it serves as a practical point of demarcation between acute and chronic critical illness.18 It is also the defining criterion of national diagnosis related groups 541 and 542 (formerly diagnosis related group 483),20 in which a large national dataset of similar patients across many institutions and settings are classified and can be compared. We excluded patients with previous ventilator dependence or RCU admission, patients from other institutions, and those without English proficiency. The institutional review board of Mount Sinai School of Medicine, New York, approved this study, and we obtained informed consent from all subjects or appropriate surrogates.

**COGNITIVE ASSESSMENT**

We conducted cognitive assessments at multiple, longitudinal time points: at study entry (after tracheotomy and transfer from ICU to RCU), biweekly in the RCU, at RCU discharge, and, for surviving patients, at 3 and 6 months after RCU discharge. These intervals included assessments while patients were mechanically ventilated and after ventilator liberation.

For RCU cognitive assessments, we used the Confusion Assessment Method for the ICU (CAM-ICU),15,21 which includes a preliminary evaluation of consciousness. A trained research nurse (A.F.M.) performed these assessments.2 To evaluate consciousness, we used the Richmond Agitation-Sedation Scale (RASS),23,24 which encompasses 10 levels (0 to +4 indicates increasing agitation and 0 to −5 indicates decreasing consciousness). We deferred delirium assessment for patients initially rated as deeply sedated (RASS level −4) or un arounable (RASS level −5), whom we classified together as comatose; we approached these patients later the same day and performed delirium assessment as possible.22 Next, we evaluated the patients for 4 basic features of delirium: (1) acute onset or fluctuating course, (2) inattention (evaluated by the Vigilance A Random Letter Test25), and (3) disorganized thinking or (4) altered level of consciousness. We defined delirium by the presence of both features 1 and 2 and either feature 3 or feature 4.26

We conducted postdischarge cognitive assessments by telephone. Because patients able to respond could communicate orally, we used the validated telephone CAM25 for this purpose.26 For patients who could not respond to telephone interviews, we asked responding surrogates about the nature of the patient’s inability to participate (cognitive or physical limitation); surrogates reported the patient’s level of consciousness and other aspects of cognitive status.

**OTHER DATA COLLECTION**

We recorded administration of analgesic, sedative, antidepressant, antipsychotic, and psychostimulant medications in the RCU to provide a context for cognitive assessments during RCU treatment. We collected additional information including diagnoses, comorbid conditions, and other data for Acute Physiology and Chronic Health Evaluation II27 and Charlson Comorbidity Index28 scores; lengths of stay; and site and ventilator status at discharge and follow-up. To measure functional status at multiple time points, we used the motor scale of the Functional Independence Measure (FIM Motor),29 which includes 13 items (eg, eating, bathing, and walking) that are each scored from 1 (needs total assistance) to 7 (complete independence); total FIM Motor scores range from 13 (completely dependent) to 91 (completely independent). Responses to telephone interviews (used for postdischarge functional assessments) and to in-person interviews (used for in-hospital assessments) are strongly correlated for the FIM Motor,29 which is well validated. In addition, we calculated the Katz Index of Activities of Daily Living.31

As a baseline for comparison with our prospective assessments of cognition and function in the hospital and after discharge, we used interviews with families or other appropriate and knowledgeable surrogates at study entry about the patient’s status during the 2 weeks before hospitalization. Cognitive status interviews focused on medical history of dementia, decreased level of consciousness, confusion, and memory loss; we also reviewed patients’ medical records for evidence of these or other cognitive disturbances. For assessment of baseline functional status, we interviewed families with respect to FIM Motor items, on which surrogate reports are well correlated with information from patients themselves.32

**STATISTICAL ANALYSIS**

We calculated mean and median daily doses of opioids (inmorphine equivalents) and of sedatives (in lorazepam equivalents) as...
the mean and median, respectively, of the individual mean daily doses given to each patient during the RCU stay. We compared patients with delirium or coma and patients without these forms of brain dysfunction with respect to the percentage of patients receiving medications in these classes and the average daily doses of these medications (χ² test and t test, respectively). We calculated duration of delirium or coma in the RCU as the number of consecutive days from the first day on which CAM-ICU assessment documented either condition. For each patient, we also calculated the percentage of total RCU days for each cognitive disturbance under study. We used multivariate logistic (discrete outcomes) and multivariate linear (continuous outcomes) regression to examine the association of number of days spent in delirium or coma with the studied outcomes. For each patient, we also calculated the mean and median of the individual mean daily doses during hospital admission.

Among 330 patients who had undergone tracheotomy and were consecutively admitted to the RCU, 230 were eligible (37, 30, 20, and 13 patients were excluded for prior ventilator dependence or RCU treatment, transfer from another hospital, language barrier, or other reasons, respectively), and 203 (88.2%) were enrolled in the study. Consent was refused by 24 patients and was not sought for 3 because death supervened. Eighty-nine surviving patients were discharged from the hospital, and all but 4 (who were lost to follow-up) were followed up for 6 months.

**RESULTS**

**PATIENT CHARACTERISTICS**

Table 1 details patient characteristics. Study patients were mainly older adults (median age, 72 years) with multiple medical illnesses and organ failures. Most, however, had been living at home and were functioning independently before their hospitalization. More than 80% (160 of 203) were reported by their families and confirmed by medical records to have no cognitive impairment. The mean (SD) Charlson Comorbidity Index score, Acute Physiology and Chronic Health Evaluation II score, and number of acute comorbid conditions at study entry were 4.5 (2.7), 20.5 (5.1), and 2.3 (2.1), respectively (ie, there was a high severity illness and comorbidity burden). By then, most patients had already been hospitalized for a long period (median duration of illness [interquartile range], 25.0 days [19.0-34.0 days]), including a prolonged ICU stay (16.0 days [11.0-22.0 days]). These patients were treated in the RCU for even longer periods (23.0 days [13.0-35.0 days]). Total duration of exposure to an intensive care environment (ICU plus RCU stay) averaged 45.0 days.

**PATIENT OUTCOMES**

Patient outcomes are presented in Table 2. Of the 203 subjects, 58 (28.6%) died in hospital and less than half (89 [43.8%]) were alive at 6 months. Of 145 hospital survivors, 15 (10.3%) were discharged to home and 107 (73.8%) to a nursing home or another acute care facility; 48 (33.1%) remained mechanically ventilated. Me-
RESULTS OF COGNITIVE ASSESSMENTS

Prevalence of coma and delirium is detailed in Table 3. At RCU admission, 50.2% of patients were comatose, and 14.8% were delirious. Approximately two thirds (53 of 85) of 6-month survivors (including 14 [43.8%] of 32 patients at home) were dependent in all activities of daily living.

POSTDISCHARGE

Follow-up data on brain dysfunction are presented in Table 3. At 6 months, 60 (70.6%) of 85 survivors, including 15 (46.9%) of 32 then living at home, remained profoundly cognitively impaired to the point that they could not participate in telephone mental status testing. Of 25 patients who could communicate by telephone, none was cognitively impaired as measured by the CAM.

MEDICATIONS

Administration of medications with the number (percentage) of 203 study patients is given in the following tabulation:

<table>
<thead>
<tr>
<th>Medication Type</th>
<th>Number (Percentage)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Opioid</td>
<td>160 (78.8)</td>
</tr>
<tr>
<td>Sedative</td>
<td>128 (63.1)</td>
</tr>
<tr>
<td>Antidepressant</td>
<td>43 (21.2)</td>
</tr>
<tr>
<td>Antipsychotic</td>
<td>125 (61.6)</td>
</tr>
<tr>
<td>Psychostimulant</td>
<td>19 (9.4)</td>
</tr>
</tbody>
</table>

The median daily doses of opioid in parenteral morphine equivalents, and of benzodiazepine (the only sedative used in the RCU) in lorazepam equivalents, were 5.1 mg/d and 1.0 mg/d, respectively. Among 62 patients who presented to the study with intact cognition—that is, neither comatose according to the RASS nor delirious according to the CAM-ICU—35 (92.1%) of 38 who remained intact received a sedative or opioid compared with 16 (100%) of 16 patients who developed brain dysfunction during the RCU stay ($P = .34$) (8 patients died in the RCU). On average, patients who were comatose or delirious received 2.4 mg/d of morphine equivalents and 1.2 mg/d of lorazepam equivalents in the 2 days prior to brain dysfunction, compared with daily doses of 6.4 mg of morphine equivalents and 1.3 mg of lorazepam equivalents in the cognitively intact group ($P = .30$ and $P = .76$, respectively). Of the 16 patients who were initially intact but developed coma or delirium in the RCU, 11 (68.7%) received sedatives, opioids, or antipsychotic drugs during the 24 hours before the first episode of brain dysfunction whereas 9 (56.2%) of 16 received these medications after the episode.
MULTIVARIATE ANALYSES

The number of days spent in delirium or coma was significantly associated with an increased likelihood of being discharged to a post–acute care facility as opposed to home (odds ratio, 1.09; 95% confidence interval [CI], 1.00-1.20; \( P = .047 \)), longer length of hospital stay (parameter estimate, 0.03; 95% CI, 0.02-0.03; \( P < .001 \) for association with longer length of stay), and lower FIM Motor scores indicating poorer functional status at 3- and 6-month follow-ups for survivors (for 3-month follow-up: parameter estimate, −0.47; 95% CI, −0.78 to −0.15; \( P = .004 \); for 6-month follow-up: parameter estimate, −0.92; 95% CI, −1.4 to −0.43; \( P < .001 \)). The association of the number of days spent in delirium or coma with 3-month survival for those who survived hospitalization was of borderline significance (odds ratio, 0.98; 95% CI, 0.95-1.00; \( P = .056 \)). Days spent in delirium or coma was not significantly associated with in-hospital mortality, likelihood of liberation from the ventilator, 6-month mortality, or 3- or 6-month site of residence.

There are now estimated to be over 100 000 chronically critically ill patients in the United States each year,\(^2,3,37\) and numbers are steadily increasing.\(^3\) These patients, who have survived but not recovered from acute critical illness, have a discrete syndrome: ongoing ventilator dependence, severe debility, and characteristic abnormalities of metabolic and immunologic function, with resulting failure of other organs and recurrent nosocomial infections.\(^4\) The present study suggests that brain dysfunction, manifest as delirium (assessed by CAM-ICU)\(^15\) and coma (levels −4 and −5 on the RASS scale), is another prominent feature of chronic critical illness. In addition, brain dysfunction in these patients is prolonged, and its duration is associated with longer lengths of stay and poorer functional status. Six months after aggressive treatment in a specialized hospital unit, three fourths of our study patients were either dead or institutionalized, and two thirds of survivors remained in hospital.

Table 3. Prevalence of Brain Dysfunction (Coma or Delirium) During Chronic Critical Illness

<table>
<thead>
<tr>
<th>Cognitive Assessment*</th>
<th>RCU Admission</th>
<th>Biweekly Assessment</th>
<th>RCU Discharge</th>
<th>Postdischarge Follow-up, Mo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RCU Admission</td>
<td>Biweekly Assessment</td>
<td>RCU Discharge</td>
<td>3</td>
</tr>
<tr>
<td>Comatose or otherwise unresponsive CAM-ICU (RASS −4 or −5)</td>
<td>102 (50)</td>
<td>77 (38)( ^\dagger )</td>
<td>58 (36)</td>
<td>75 (77)( ^\ddagger )</td>
</tr>
<tr>
<td>CAM (telephone)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Delirious</td>
<td>30 (15)</td>
<td>56 (28)( ^\S )</td>
<td>21 (13)</td>
<td>0</td>
</tr>
<tr>
<td>Always</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥50% and &lt;100% of assessments</td>
<td>22 (11)</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>&lt;50% of assessments</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not delirous or comatose</td>
<td>62 (30)</td>
<td>63 (31)</td>
<td>76 (48)</td>
<td>23 (23)</td>
</tr>
<tr>
<td>Refused to respond</td>
<td>8 (4)</td>
<td>6 (3)</td>
<td>5 (3)</td>
<td>0</td>
</tr>
<tr>
<td>Total patients</td>
<td>202</td>
<td>202</td>
<td>160</td>
<td>98</td>
</tr>
</tbody>
</table>

Abbreviations: CAM, Confusion Assessment Method; ICU, intensive care unit; RASS, Richmond Agitation-Sedation Scale; RCU, respiratory care unit.

*We assessed brain dysfunction using the CAM-ICU\(^15\) incorporating the RASS.\(^23,24\) Patients rated as level −5 (unarousable) or −4 (deeply sedated) on the RASS (classified together as comatose) lacked sufficient consciousness for further evaluation of delirium at that assessment.

†We categorized as comatose those patients who were rated as RASS level −4 or −5 at 75% or more of our biweekly approaches.

‡We used the validated telephone CAM\(^25\) for postdischarge evaluations.

§For patients able to respond to CAM-ICU (ie, not comatose on the initial RASS evaluation) at more than 25% of the biweekly approaches, we categorized as delirious those patients found to have at least 1 episode of delirium, and we categorized as not delirious those patients who were never found to be delirious. Some patients categorized as delirious or not delirious for the biweekly assessments may have had 1 or more episodes of coma (but <75% of the CAM-ICU approaches) during this period.

↑One patient was not approached for cognitive assessment at RCU admission or during biweekly approaches, and 4 among 164 RCU survivors were discharged before completion of the assessment. The numbers of patients for 3-month and 6-month follow-ups were 98 and 85, respectively, as explained in the previous 2 footnotes.

Figure. We used the Richmond Agitation-Sedation Scale\(^23,24\) and the Confusion Assessment Method for the Intensive Care Unit\(^15,35\) for biweekly cognitive assessments, as detailed in the “Methods” section. The bar graph shows results of these assessments for 202 study patients through week 4 in the respiratory care unit (RCU) (average length of RCU stay, 3 to 4 weeks).

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mained profoundly cognitively impaired whereas most of these patients had been at home, independent, and without cognitive impairment prior to hospitalization. Less than 10% were living at home without brain dysfunction as measured by CAM at 6 months. Findings of this study have important implications for decision making.

Delirium occurs commonly in ICU patients with acute critical illness and is associated with longer hospital and ICU lengths of stay and higher mortality at 6 months. Our data suggest that patients who survive the ICU but remain ventilator dependent with chronic critical illness have similarly high rates of delirium as well as coma. However, unlike ICU delirium (which has a median duration of 48 hours), these conditions persist in the chronically critically ill for a prolonged period. This occurs despite the fact that doses of sedating drugs are generally lower after tracheotomy and during ventilator weaning.

In our study, 65.3% of patients were admitted to the RCU with coma or delirium, more than 25% of those who were initially without coma or delirium developed these conditions in the RCU, and less than half of both groups combined regained normal cognition.

Cognitive impairment is often considered to be the heaviest burden of illness and is an outcome that may be even less acceptable than death. Patients, families, and clinicians consider information about expected cognitive outcome to be important specifically for decision making. Findings of this study have important implications for decision making and thereafter with these severe forms of brain dysfunction.

There are several limitations to this study. We performed our research in a single hospital's in-patient RCU. Our findings may not apply to patients who have undergone tracheotomy and whose illness is so severe that they cannot survive outside of an ICU (like those in our hospital who underwent tracheotomy but died in the ICU before transfer to the RCU) or those who undergo tracheotomy with the understanding that they are not expected to be liberated but rather to remain mechanically ventilated indefinitely (like those in our hospital who are not referred to the RCU because they are clinically determined to be unweanable). Our eligibility criteria, however, were designed to encompass a broad and generalizable group of patients requiring prolonged mechanical ventilation via tracheotomy after failure to wean in the ICU. Although treated in various care settings (long-term acute care facilities and skilled nursing facilities as well as inpatient hospital units), chronically critically ill patients have comparable characteristics and outcomes, as reported from multiple institutions and reflected in the national diagnosis related group 541-542/483 database.

We have described our experience with a large series of patients initially treated in a variety of ICUs, of whom we made over 1700 delirium assessments using instruments (CAM-ICU and RASS) that were rigorously tested in prior work. Because the CAM-ICU was already validated in 2 patient groups, we did not retest it against a reference standard but instead focused on use with a discrete group of patients with prolonged illness and mechanical ventilation. In follow-up after RCU discharge, we used the original CAM (validated telephone version), which is more sensitive than CAM-ICU for diagnosing delirium in nonintubated patients. The number of patients who could respond to cognitive assessment after hospital discharge was limited by the high rates of mortality and institutionalization; patients able to respond to telephone interview were less likely to have delirium and other forms of cognitive impairment than nonresponders, which would have underestimated the true prevalence of post-discharge delirium in the entire study population.

**CONCLUSIONS**

As the general population ages and intensive care treatments are offered to older and sicker patients, clinicians in all fields and disciplines will encounter chronically critically ill patients with increasing frequency. Most of these patients die within 6 months, and most survivors are institutionalized with severe functional impairments. Our previous research indicates that most patients with chronic critical illness spend weeks to months in the hospital experiencing a multitude of distressing physical and psychological symptoms. The present study suggests that few patients with chronic critical illness avoid delirium or coma and that most of them spend significant time during treatment and thereafter with these severe forms of brain dysfunction. Although regular, comprehensive assessment and treatment of symptoms may reduce suffering, it is less clear that effective treatments exist to address the high prevalence of brain dysfunction observed here. Nor can we be certain that such treatments would improve mortality rates or functional outcomes.

The choice to continue life-prolonging treatments when critical illness enters a chronic phase may be made by some patients and families despite poor prognosis for survival and for cognitive and functional recovery. However, accumulating evidence of symptom distress and long-term cognitive and functional impairment calls attention to whether they are truly making informed decisions at the time of tracheotomy and whether ongoing goals of care are routinely discussed during the course of critical illness.

Future research should focus on strategies to alleviate symptom burden and to address delirium and other brain dysfunction. In addition, it is essential to examine how information is communicated and how decisions are made about the benefits and burdens of life-prolonging therapies (eg, mechanical ventilation) for the chronically critically ill. In the meantime, options presented to decision makers for these patients should include a time-limited trial of continued respiratory support, with a plan for discontinuation of the ventilator if cognitive and functional recovery do not occur within a reasonable period of time. The levels of disease complexity, physical and psychological suffering, and cognitive impairment also suggest that quality care for these patients should include not only expert pulmonary and critical care but also involvement of a palliative care consultation team.

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REFERENCES