CME CREDIT *EDUCATIONAL OBJECTIVE:* Readers will assess their patients in the intensive care unit for the development of cognitive impairment and consider ways to prevent it

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Cognitive impairment in ICU survivors: Assessment and therapy

ABSTRACT

Cognitive impairment occurs in up to one-third of intensive care patients and may affect one or more cognitive domains. Because data are scarce on therapies for this complication, prevention remains the prevailing strategy. In this review, we discuss the clinical approach to cognitive impairment after an intensive care unit (ICU) stay.

KEY POINTS

The development of cognitive impairment during hospitalization has been associated with complications such as hypotension, hyperglycemia, hypoxemia, and delirium.

The "ABCDE" strategy is used to prevent delirium, although its effect on cognitive impairment has not been proven. ABCD stands for **a**wakening and early spontaneous **b**reathing, **c**hoice of sedatives with fewer adverse effects (ie, avoidance of benzodiazepines and opioids), **d**aily delirium monitoring, and **e**arly mobility exercise.

Cognitive impairment is usually diagnosed using restrictive or comprehensive evaluation tools. The Montreal Cognitive Assessment is probably the one most often used since it is readily available, simple, and reliable.

Most of the evidence on treating cognitive impairment after an ICU stay is extrapolated from studies in patients with mild cognitive impairment or traumatic brain injury. Cognitive training has shown positive results, mostly in improvement of memory, particularly immediate recall.

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Intensive care medicine has dramatically evolved over the last 15 years, after reports from many landmark trials.[1] Updated strategies for mechanical ventilation[2] and "bundles" of strategies to optimize hemodynamic therapy[3] have reduced the rates of morbidity and death from deadly critical conditions such as the adult respiratory distress syndrome (ARDS) and sepsis.

Despite these important improvements in short-term outcomes, it is increasingly recognized that intensive care unit (ICU) survivors suffer considerable long-term complications that affect their usual functioning.[4] Recently, the Society of Critical Care Medicine convened a conference in which these long-term complications were named the "post-intensive care syndrome."[5]

Quality of life, particularly its physical component, is considerably lower after a stay in the medical or surgical ICU.[6–8] Posttraumatic stress disorder, depression, and sexual dysfunction are consistently reported years after ICU discharge.[9–13]

Perhaps the most frequently unrecognized complication in ICU survivors is cognitive impairment. Current data suggest that neurocognitive impairment after an ICU stay is common and that it persists 6 years or more after hospital discharge.

Hopkins et al[14,15] analyzed 10 cohort studies of long-term cognitive impairment after an ICU stay; 5 of them focused on patients with ARDS. The prevalence of cognitive impairment was as high as 78% at hospital discharge, 46% at 1 year, and 25% 6 years after discharge.[15,16] Of the cognitive domains compromised, memory was the most often affected, followed by executive function and attention.[14,17]

Interestingly, data suggest that cognition may improve somewhat in the first 6 to 12 months after ICU discharge.[15] Therefore, if we can detect it early on and promptly refer patients for cognitive therapy, we may eventually improve the prognosis of this disabling complication.

This review will focus on how to evaluate, prevent, and treat cognitive impairment in patients who survive an ICU stay.

COGNITIVE IMPAIRMENT AFTER A STAY IN THE ICU

The association between ICU stay and neurocognitive dysfunction is poorly understood. Potential causes include hypoxemia,[18] hypotension,[19] hyperglycemia,[14] and—an area of growing interest and evolving research—sedation and delirium.[20]

Patients on mechanical ventilation are commonly given sedatives and analgesics to prevent anxiety and pain.[21] However, these medications are strongly associated with delirium.[22] In fact, recent studies found that benzodiazepines have an independent, dose-related, temporal association with delirium, with some reports describing a 20% increase in delirium per milligram of benzodiazepine.[23] In another study, which included medical and surgical ICU patients, use of morphine was the strongest predictor of delirium, with a sixfold increase in odds over a period of 5 months.[24]

Cognitive impairment is perhaps the most frequently unrecognized complication in ICU survivors

Delirium is important to prevent, diagnose, and treat, since it has a direct association with the development of long-term cognitive impairment.[22,25] A review of studies that included 1,885 medical and surgical patients found that those who developed delirium during an ICU stay were three times more likely to have cognitive dysfunction when assessed 3 years later.[20]

Whether delirium is a primary disorder associated with cognitive impairment or if it only represents an underlying process leading to poor cognitive outcomes is unknown. As delirious patients are more likely to be older, to be mechanically ventilated, to require more sedation, and, in particular, to be sicker, the association between delirium and cognitive impairment may reflect the relationship between these risk factors and poor cognitive outcomes.[26]

Glucose and its relationship with cognitive function is another topic of investigation. A secondary analysis of a study that included ARDS survivors revealed that blood glucose values higher than 153 mg/dL, higher glucose variability, and duration of mechanical ventilation were associated with cognitive sequelae.[27,28]

Other studies focused on mechanical ventilation. In one study,[29] one-third of patients who had been mechanically ventilated showed signs of neurocognitive impairment when they were evaluated 6 months after hospital discharge.

Mild cognitive impairment differs from cognitive impairment after an ICU stay

Cognitive impairment after ICU discharge does not follow the same pattern as mild cognitive impairment, and some authors consider these two types of cognitive impairment to be unrelated.

While mild cognitive impairment is progressive and associated with aging, cognitive impairment in ICU survivors develops rapidly after acute illness and is usually related to numerous pathologic and neurochemical pathways.

For example, the neurotransmitter acetylcholine is thought to be involved in cognitive function as well as neuroplasticity of the motor cortex. In a model of cognitive impairment after stroke, activity of the cholinergic system was reduced.[30,31] Further, in a study in rats, Baskerville et al[32] showed that experience-dependent plasticity could be completely blocked by damaging the cholinergic neurons in the nucleus basalis of Meynert, thereby affecting memory and other functions supported by this pathway.

Another implicated pathway involves dopamine. Of interest, dopamine augmentation has been shown to enhance simple motor memories and to improve procedural learning. Understanding of these neurochemical alterations opens opportunities for investigation of drug therapies.

ASSESSMENT TOOLS

Cognitive impairment is important to detect in ICU survivors because it predicts poor outcomes from rehabilitation. A study of stroke

patients found that those with cognitive alterations immediately after the stroke were less likely to be discharged home or to be living at home 6 months after discharge.[33]

A possible explanation may be that affected patients cannot fully participate in rehabilitation activities, owing to impairment in executive function, inability to remember therapy instructions, or disruption of implicit and explicit learning. Indeed, some authors consider cognitive impairment after acquired brain injury to be the most relevant surrogate marker of rehabilitation potential. Consequently, manipulation or enhancement of cognition may directly affect rehabilitation outcomes.[34]

Disagreement about terminology and diagnostic criteria creates a problem for health care providers working with patients with potential cognitive impairment. Numerous systems have been proposed to define this condition; in fact, Stephan et al[35] reviewed the literature and found no fewer than 17. None of them is specific for cognitive impairment after an ICU stay.

Petersen et al[36] in 1999 proposed initial criteria for mild cognitive impairment that included the following:

- A memory complaint
- Normal general cognitive functioning
- Normal activities of daily living
- Memory impairment in relation to age and education
- No dementia.

Later, other areas of impairment besides memory were recognized, such as language, attention, perception, reasoning, and motor planning.[37] Therefore, mild cognitive impairment is currently classified into subtypes, which include amnestic (affecting single or multiple domains) and nonamnestic (also affecting single or multiple domains).[38]

In clinical practice, impairment of specific cognitive domains may be challenging to detect, and neuropsychological testing is often needed. Cognitive screening tests can detect impairment across a restricted range of cognitive abilities, while more comprehensive assessments address each of the primary domains of cognition.[39] Formal testing provides normative and validated data on cognition performance and severity.

The Montreal Cognitive Assessment[40] is popular, comprehensive, used in a variety of professions in diverse types of facilities (acute care, rehabilitation, and skilled care facilities), and brief (taking 11 minutes to administer). It evaluates orientation, memory, language, attention, reasoning, and visual-constructional abilities. The maximum score is 30; cognitive impairment is defined as a score of less than 26. It has a sensitivity of 90% and a specificity of 87%.

The Folstein Mini-Mental State Examination (MMSE) is the most commonly used of the noncomprehensive tests in clinical practice.[41] It assesses orientation, memory, language, attention, and praxis. It has a maximum score of 30 points; the cutoff score for cognitive impairment is 24 points or less.

A limitation of the MMSE is that its sensitivity is very low, ranging from 1% to 49%.[42,43] The MMSE scores of patients with cognitive impairment overlap considerably with those of age-matched healthy controls.[39] Conversely, the MMSE's specificity is usually high, ranging from 85% to 100%.[42]

Moreover, the MMSE poses copyright issues, an important consideration when selecting a test. In 2001, the authors of the MMSE transferred all intellectual property rights to Psychological Assessment Resources, which has exclusive rights to publish, license, and manage all intellectual property rights in all media and languages. Photocopying and using the MMSE without applying for permission from and paying this company ($1.23 per use) constitutes copyright infringement. Therefore, health care providers and researchers have been using other tests to evaluate cognition.

Some reports describe a 20% increase in delirium per milligram of benzodiazepine

Other tests of cognition assess individual domains. Interestingly, studies of long-term cognitive impairment after ICU admission used these tests to define outcomes.[25] Specific tests include:

- The Digit Span and the Trailmaking Test A (used to assess attention and orientation)[25]
- The Rey Auditory Verbal Learning Test (used to evaluate verbal memory)
- The Complex Figure Test (helpful in defining visual-spatial construction and delayed visual memory)

- The Trailmaking Test B (also included in the Montreal Cognitive Assessment; assesses executive functioning).

Besides formal testing, an informal battery is often recommended to provide additional information. An informal evaluation includes word definition, reading and verbal fluency, reading comprehension, and performance of instrumental activities of daily living. Observing as patients perform tasks of daily living provides therapists with a vast amount of information, as these tasks require using multiple cognitive processes. Therefore, if a functional breakdown occurs during this assessment, the clinician needs to identify the domain or specific level of cognitive dysfunction involved in that deficit.[44]

PREVENTIVE STRATEGIES

Strategies for minimizing the long-term effects of cognitive impairment have mostly focused on preventing it.

During the ICU stay, optimizing hemodynamic, glucose, and oxygenation levels may prevent future long-term complications.[18]

Also, the association between sedation, delirium, and consequent cognitive impairment (see above) has led many investigators to apply the "ABCDE" bundle of strategies.[25,45,46] Specifically, ABCDE stands for **a**wakening and **b**reathing, **c**hoice of sedatives with fewer adverse effects, **d**aily delirium monitoring, and **e**arly mobility exercise. These strategies have been shown in randomized controlled trials to prevent delirium; however, they have not been proved to prevent cognitive impairment.

The Mini-Mental State Examination is copyrighted; therefore, providers have been using other tests

Awakening and breathing

In the Awakening and Breathing Controlled Trial,[47] patients in the intervention group (ie, those who had their sedatives interrupted every morning to see if they would awaken, and if so, if they could breathe on their own) were extubated 3 days sooner than those in the control group (who underwent daily trials of spontaneous breathing, if deemed safe). Also, ICU and hospital length of stay were shorter by 4 days. Best of all, over 1 year, the mortality rate was lower by 14 absolute percentage points.

Choice of sedatives

Often, mechanically ventilated patients are given benzodiazepines, opiates, and propofol (Diprivan).[21] Dexmedetomidine (Precedex), a newer agent, is an alpha-2 agonist and may offer advantages over the others.

To date, three randomized controlled trials have assessed the effect of dexmedetomidine in terms of outcomes associated with delirium, and one trial evaluated its association with intellectual capacity in ICU patients.

The Maximizing Efficacy of Targeted Sedation and Reducing Neurological Dysfunction (MENDS) trial randomized patients on mechanical ventilation to receive either dexmedetomidine or lorazepam (Ativan).[48] Dexmedetomidine-treated patients had 4 more days alive without delirium or coma (7 vs 3 days, $P = .01$).

Subsequently, the **Safety and Efficacy of Dexmedetomidine Compared With Midazolam (SEDCOM) trial** compared dexmedetomidine and midazolam (Versed) in mechanically ventilated patients. Those who received dexmedetomidine had a lower incidence of delirium (54% vs 76%, $P < .001$), and 2 fewer days on mechanical ventilation.[49]

Reade et al[50] evaluated time to extubation in already delirious patients randomized to receive either dexmedetomidine or haloperidol (Haldol). Those receiving dexmedetomidine had a shorter time to extubation as well as a shorter ICU length of stay.

The Acute Neuroscience Intensive Care Sedation Trial[51] evaluated intellectual capacity in neurological ICU patients sedated with either dexmedetomidine or propofol. This randomized, double-blind trial included 18 brain-injured and 12 non-brain-injured intubated patients. In a crossover protocol, each received the combination of fentanyl (Sublimaze) and propofol and the combination of fentanyl and dexmedetomidine.

Cognition was evaluated using the Adapted Cognitive Exam (ACE), which assesses intellectual capacity through orientation, language, registration, attention, calculation, and recall. This 10-minute examination does not require verbal communication, as it relies on the ability to respond to yes-or-no questions and perform simple motor tasks. The maximum possible score is 100 points.

Interestingly, while on propofol, the patients' adjusted ACE scores went down by a mean of 12.4 points, whereas they went up by 6.8 points while on dexmedetomidine. Even though brain-injured patients required less sedation than non-brain-injured patients, the effect of dexmedetomidine and propofol did not change.[51]

In summary, these studies suggest that all sedatives are not the same in their short-term and intermediate-term outcomes.

In our practice, we use dexmedetomidine as our first-line sedation therapy. In patients with hemodynamic instability, we use benzodiazepines. We reserve propofol for very short periods of intubation or for hemodynamically stable patients who cannot be sedated with dexmedetomidine.

Daily delirium monitoring

As mentioned above, delirium affects many patients on mechanical ventilation, and it is highly underrecognized if valid tests are not used.[52] Therefore, it is critically important to be familiar with the tests for assessing delirium. Of these, the Confusion Assessment Method for the ICU is probably the one with the best performance, with a sensitivity of 93% to 100% and a specificity of 98% to 100%.[53,54]

Early mobilization

A landmark study paired the awakening and breathing strategy with early mobilization through physical and occupational therapy in the ICU.[55] Patients in the intervention group had a higher rate of return to independent functional status upon hospital discharge and a shorter duration of mechanical ventilation and delirium.

In conclusion, even though direct prevention of cognitive dysfunction is a challenging task, the ABCDE approach targets individual risk factors for delirium, which is an important contributor to cognitive impairment. Whether the ABCDE bundle directly affects the development of cognitive impairment requires further investigation.

COGNITIVE THERAPIES

The cognition-focused intervention most often described is cognitive training. Cognitive training is delivered in individual or group sessions in which the patient practices tasks targeting different domains, such as memory, language, and attention. Outcomes are often assessed in terms of improvement in test scores or effects on everyday functioning. Unfortunately, because of heterogeneity among cognitive training interventions and studied populations, we cannot yet make strong evidence-based recommendations for clinical practice.

Martin et al[56] in 2011 reviewed cognition-based interventions for healthy older people and people with mild cognitive impairment and found 36 relevant studies. Of these, only 3 were in patients with mild cognitive impairment, while the rest were in healthy older people.[56–58] Overall, the only available data were related to the memory domain, and outcomes were mostly associated with immediate recall of words, paragraphs, and stories. Based on this, cognitive therapy is currently considered justified, as most patients with cognitive impairment after an ICU stay have memory problems.

Zelinski et al[59] conducted a randomized, controlled, double-blind study comparing outcomes in an intervention group that underwent a computerized cognitive training program with those in a control group that viewed videos on a variety of topics such as literature, art, and history. The intervention, based on brain plasticity, aimed to improve the speed and accuracy of auditory information processing and to engage neuromodulatory systems. Some of the secondary outcomes favored the intervention group. These outcomes were related mostly to measures of overall memory, such as immediate and delayed recall, but also to a composite outcome that included letter-number sequencing and the digit span backwards test.

A landmark study paired the awakening and breathing strategy with early mobilization

Despite these encouraging results, it is worth mentioning that these studies were not performed in patients with cognitive impairment associated with ICU admission. Therefore, the applicability and effectiveness of such therapies in post-ICU patients remains unknown.

Patients with posttraumatic brain injury and stroke have also been extensively studied in regard to the development of cognitive im-

pairment.[34] These patients probably represent a better standard for comparison, as their cognitive impairment does not necessarily progress.

The effect of cognitive rehabilitation on the recovery in these patients depends on *adaptation* and *remediation*. Adaptation describes a patient's ability to compensate for functional impairment.[34] This can be divided into internal and external adaptation. Internal adaptation requires the patient to recognize his or her cognitive limitation in order to adapt the to the environment accordingly. External adaptation entails getting help from devices or relatives (eg, phone calls) to achieve desired goals (eg, taking medication at scheduled times). Again, to adapt, the patient needs to be able to recognize his or her affected cognitive domain. Unfortunately, this is not always the case.

Remediation refers to the actual regaining of a lost ability. To stimulate neural plasticity, the patient is required to experience and repeat targeted skill-building activities.[38] There is evidence that patients are more likely to regain lost ability by repeating the practice frequently during a short period of time.[60]

From the physician's perspective, evaluating and identifying deficits in particular cognitive domains may help in designing a remediation plan in partnership with a cognitive therapist.

Despite encouraging results, we cannot yet make evidence-based recommendations for cognitive therapy

Cognitive rehabilitation in ICU survivors

The Returning to Everyday Tasks Utilizing Rehabilitation Networks (RETURN) study focused on cognitive and physical rehabilitation in post-ICU patients.[61] This pilot study included 21 ICU survivors with cognitive or functional impairment at hospital discharge. Eight patients received usual care and 13 received a combination of in-home cognitive, physical, and functional rehabilitation over a 3-month period with a social worker or a master's-level psychology technician.

Interventions included six in-person visits for cognitive rehabilitation and six televisits for physical and functional rehabilitation. Cognitive training was based on the goal-management training (GMT) protocol.[62] This strategy attempts to improve executive function by increasing goal-directed behavior and by helping patients learn to be reflective before making decisions and executing tasks. The GMT model consists of sessions that build on one another to increase the rehabilitation intensity. During each session, goals are explained and participants perform increasingly challenging cognitive tasks.

Cognitive outcomes were evaluated using the Delis-Kaplan Tower Test to evaluate executive function by assessing the ability to plan and strategize efficiently. The patient is required to move disks across three pegs until a tower is built. The object is to use the fewest moves possible while adhering to two rules: larger disks cannot be placed on top of smaller ones, and disks must be moved one at a time, using only one hand.

At 3 months there was a significant difference between groups, with the intervention group earning higher tower test scores than controls did (median of 13 vs 7.5).

The Activity and Cognitive Therapy in the Intensive Care Unit (ACT-ICU) trial is another pilot study that will attempt to assess the feasibility of early cognitive rehabilitation in ICU survivors. This study will combine early mobilization with a cognitive intervention, and its primary outcome is executive function (with the tower test) at 3 months after discharge.[63]

DRUG THERAPY

Some medications have been tested to assess whether they reduce the risk of progression from adult traumatic brain injury to cognitive impairment. These drugs augment dopamine and acetylcholine activity.

Methylphenidate (Ritalin), a dopaminergic drug, was studied in two trials. The first was a double-blind trial in 18 patients with posttraumatic brain injury. Memory was found to improve, based on the Working Memory Task Test. However, due to the small number of participants, no further conclusions were obtained.[64]

The second trial, in 19 patients with posttraumatic brain injury, had a double-blind crossover design. Attention, evaluated by the Distraction Task Test, improved with the use of methylphenidate.[65] Again, the small number of patients precludes generalization of these results.

Donepezil (Aricept), a cholinergic drug, was evaluated in four clinical trials in posttraumatic brain injury patients[66–69]; each trial included 21 to 180 patients. The trials evaluated the drug's effect on memory and attention through a variety of tools (Paced Auditory Serial Addition Test; Wechsler Memory Scale; Boston Naming Test; Rey Auditory Verbal Learning Test; Complex Figure Test; and Reaction Time–Dual Task). Interestingly, donepezil was associated with large improvements in objective assessments of attention and memory. Despite methodologic flaws, such as a lack of blinding in one of these studies[69] and an open-label design in two of them,[66,68] of the drugs available, donepezil presents the strongest evidence for use in cognitive impairment after traumatic brain injury.[70]

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