CHAPTER 151  ■  ICU DISCHARGE CRITERIA AND REHABILITATION POTENTIAL FOR SEVERE BRAIN INJURY PATIENTS

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DEFINITION OF ALTERED MENTAL STATUS AFTER SEVERE TRAUMATIC BRAIN INJURY

Severe brain injury is defined as a condition with coma, scored by the Glasgow coma scale (GCS) (1) as equal to or less than 8 for at least 6 hours (2). Severe brain injury has also been defined as a coma condition with a GCS equal to or less than 8, either initially or after deterioration, within 48 hours of injury (3). In the acute phase, the severity of coma is universally scored by means of the GCS, which differentiates mild, moderate, and severe brain injury, respectively, with scores of 13 to 15, 9 to 12 and ≤8 for severe brain injury. Although this scale is the most commonly used in the intensive care unit (ICU), other severity indexes such as the Innsbruck coma scale (ICS) have demonstrated a higher predictive power for mortality because of the inclusion of brainstem reflexes as a predictive value (4). For a detailed description of the most commonly used coma scales, see Frowein and Firsching (5) and Dolce and Saxbon (6).

Coma

The definition of coma includes the clinical triad of “closed eyes, not obeying simple commands, no comprehensible verbal utterances” (7). Coma has also been defined as a complete failure of the arousal system, with no spontaneous eye opening in patients who are unable to be awakened by application of vigorous sensory stimulation (8).

Although the assessment of impaired consciousness has been greatly facilitated by the development of the GCS, the presence of an artificial airway and ocular swelling often prevents assessment of the verbal score and complicates evaluation of eye opening; for these reasons, the grading of severely injured patients is largely, if not entirely, dependent on the motor score (9).

Coma can be associated with respiratory insufficiency, dysautonomic syndrome, and immunologic depression, especially during severe and prolonged disturbances of consciousness (6,10,11). Furthermore, specific clinical features can be observed during the rehabilitation phase, such as muscular hypertonia, dysautonomic symptoms, psychomotor agitation, and tracheopharyngeal dysfunction (12,13).

Recurrent respiratory failure is not uncommon. Although appropriate ICU discharge guidelines should include liberation from mechanical ventilation for at least 48 hours (14), 25% of the patients will require re-establishment of some form of assisted ventilation (15,16).

Severe brain injury patients often need a central venous access, an enteral feeding tube, or a percutaneous endoscopic gastrostomy (PEG). Comatose patients in the rehabilitation phase...
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Prolonged immobilization in the ICU may cause pressure skin decubitus, muscle contractures, ankylosis, and para-articular ossification (19–22), together with muscular atrophy and critical illness polyneuropathy (CIP) (23,24); the latter complication is commonly associated with sepsis. Immediate motor rehabilitation should be applied by means of adequate positioning, which should contrast pathologic postures and promote passive range of motion and basal stimulation.

Sensory deprivation related to a long stay in ICU may also reduce a patient’s interaction with the environment in the early phases of coma recovery, especially in the presence of behavioral disturbances, such as psychomotor agitation or inertia, aggravated by the limited contact of the patient with the family. A friendly environment can significantly improve a patient’s interactions. For example, a music-based therapeutic approach (25) has been associated with improved neurophysiologic parameters (26).

The term prolonged coma (PC) may be an indicator of very severe brain injury for those patients with unconsciousness duration of at least 15 days (27,28). Arousal and vigilance (eyes opening) is generally noted after 3 to 4 weeks from coma onset, either with recovery of awareness (awakening) or without recovery of consciousness (vegetative state) (29,30).

Vegetative State

The vegetative state (VS) is a condition that follows coma, when the patient recovers the vigilance or alertness (eyes opening) but not the awareness, i.e., the ability to obey simple commands. The patient, in fact, is unable to interact with the surroundings, in spite of the eyes opening and the recovery of the sleep/wake cycle. The terms “persistent” or “permanent” are no longer used to avoid inaccurate prognostic adjectives (31). In fact, consciousness recovery after 1 year has been reported in up to 10% of the cases in traumatic VS and 3% of the cases in nontraumatic VS (32). Similarly, misdiagnosis of VS has been frequently described (33), as secondary to sedative drugs or subclinical seizures, with 6.3% of them displaying a nonconvulsive status epilepticus (34).

The locked-in syndrome (LIS) is defined as a condition ap- parently similar to VS, because of the presence of quadriplegia, mutism, and paralysis of the mouth, lips, and tongue, but it is distinguished from VS because of an extended palsy to ocular motility (35). Minimally responsive state (49), has been recently introduced to identify those patients who are occasionally able to obey simple commands (50,51). This clinical state may follow either coma or VS as a transitional or permanent condition between VS and severe disability (52–54).

MCS patients demonstrate discernible behavioral evidence of consciousness but remain unable to reproduce this behavior consistently (50,51,55,56). Nevertheless, the distinction between VS and MCS is not always so clear, because of possible oscillations of the disturbance of consciousness due to different coexisting neurologic (34) and neurosurgical (37) conditions (34) or drug side effects (58,59).

Psychomotor agitation, aggressiveness, and sexual disinhibi- tion (Klüver-Bucy syndrome) are frequent behaviors in severe brain injury patients who are not able to reliably follow simple commands, and their early occurrence is a positive predictor of consciousness recovery (59,60). Few published cases sug- gest that clinical examination may not be sufficient to frame the patient’s unconsciousness state.

As for the differential diagnosis between VS, MCS, and LIS, Owen et al. (61) recently described the case of a young woman who sustained a severe head injury in a traffic accident with clinical evolution to VS. Though the VS persisted (48), an in- vestigation by means of magnetic resonance imaging (MRI) scans 5 months after the accident showed a retained ability to process language and maintain complex visual imagery as in healthy subjects (61,62). Since it has also been reported that occasional LIS patients are not able to communicate by eye- lid movements because of an extended palsy to ocular motility (63), in such cases a clinical differentiation between VS and LIS becomes and should be supported at least by an EEG, an examination not reported in this last case (62).

In the postacute phase of the patient with VS and MCS, the disability rating scale (DRS) (64), the Rancho Los Amigos scale, also defined as levels of cognitive functioning (LCF) (65) (Ap- pendix), the Coma Recovery Scale (CRS) (49), and the Wessex...
Head Injury Matrix (66) are among the scales able to monitor minimal behavioral changes during consciousness recovery. For a more extensive description of the coma and disability scales for the evaluation of severe brain injury patients, see Gill-Thwaites and Munday (67), Formisano et al. (68), Dolz and Saxton (6), and Koren et al. (69).

**EPIDEMIOLOGY**

Intensive care units (ICUs) often admit patients suffering from coma not only of traumatic cause, but also of different causes such as hypotensive or dysrhythmic cardiac arrest, ischemic or hemorrhagic stroke, central nervous system (CNS) infections and intoxications, and organic brain diseases. Epidemiologic data on coma incidence and prevalence are very poor because of the various causes of coma and the different evolution toward recovery.

Severe traumatic brain injury (TBI), mainly secondary to road accidents, represents the first cause of disability in the young population between 15 and 35 years of age, which is the more productive age range, with longer life expectancy (70–72).

Data collected in Europe (Italy) that report that TBI affects 300 new cases every 100,000 subjects per year, with a total of 1,500,000 new cases every year (73–75). One percent to 2% of the patients persist in coma for longer than 1 month. Data extrapolated from the United Kingdom (76) estimate a prevalence of disability secondary to traumatic coma of 35,000 individuals every year. In the United States, the number of individuals who sustain severe TBI with prolonged loss of consciousness each year is estimated to be between 56 and 170 per one million population (PM) (55,76,77). In the United States, of the nearly 400,000 individuals with a head injury who are admitted to a hospital each year, at least 98,000 will be significantly disabled (78,79).

The incidence of VS continuing for at least 6 months after the accident rises at a rate between 5 and 25 PM per year. In the United States, the incidence and the prevalence of MCS have yet to be established (52).

Official national statistics are not available for these conditions, since neither VS nor MCS is a formal diagnosis under DSM-IV-TR (80) or ICD-10 (81). Conversely, VS has been included and coded in the International Classification of Functioning (ICF) (82). More recent data from an Italian study group (83) calculated an incidence for VS at 6 months after coma lasting longer than 1 year had sustained a further secondary hypoxic damage. In fact, it has been reported that 90% of adults who sustained severe brain injury can show evidence of brain hypoxic ischemia at autopsy (97). GCS and duration of coma are universally considered clinical predictive indicators of the final outcome (2,53).

As soon as the patient becomes responsive, in the early phases after coma recovery, agitation and restlessness are frequent and typical of delirium complaints, which generally are a specific characteristic of posttraumatic amnesia (PTA) and coincides with level 4 of the ICF scale (confused-agitated). PTA is defined as the period of time after coma recovery when the patient is not able to memorize everyday events of the last 24 hours (98). This period may last from twice to four times the coma duration (72) and is universally considered one of the most significant predictive factors for the final outcome of severe brain injury patients (9,99). Added behavioral features of PTA may include aggression, akathisia, disinhibition, and emotional liability (100).

The presence of brainstem reflexes in the acute phase have also been reported as important clinical prognostic factors (2,9,101). The 1-year mortality after severe TBI is reported to be 86% with absent pupillary response and 90% when both pupillary reaction and oculocephalic response are absent. When both responses are absent for more than 24 hours, the death rate is 100% (102). Eye movements are a useful diagnostic discriminant (103–105), and the absence of the normal oculocephalic reflex is widely considered a sign of very poor prognosis (105,106).

In the acute and postacute phase, possible endocrinologic disorders should be investigated since hypopituitarism may need specific hormone replacement therapy (107,108). Vigilance disorders, hydroelectricity alterations, immunologic deficits, dysautonomic vegetative symptoms, and cognitive and behavioral disturbances may be secondary to selective or total dysfunction of the hypothalamic-pituitary axis (109–119).

Other predictors of poor long-term functional prognosis include decortication and decerebration postures (6,35) and vegetative dysautonomia (6,11,37). The result is difficulty in the passive range of motion, with muscle contractions and ankylosis at the level of the major joints frequently complicated by periarticular ossification (PAO) and tendon retractions or shortening (19–22,120).

In VS patients, the appearance of primitive oral automatisms, such as chewing, sucking, and yawning, may be negative predictive features for consciousness recovery (6). Conversely, psychomotor agitation and bulimia during recovery from coma and VS may be considered good prognostic indicators for the final outcome (59), as is the presence of the Klüver-Bucy syndrome, a transitory behavioral disinhibition, increased...
primitive oral automatisms, and hypersexuality (60,121,122).

Motor recovery, when present, generally starts from the distal to proximal limb, likely because of the relative sparing of the cerebral cortex, where the hand and foot are largely controlled. Asymmetric motor recovery can also represent undiagnosed spinal cord injury, or CIP, or it may be linked to hydrocephalus (57), especially if associated to epileptic seizures, and cognitive and behavioral disturbances poorly responsive to pharmacologic and rehabilitative treatment. Finally, myoclonic jerks may be secondary to cortical or brainstem lesions or cerebral hypoxic damage with unfavorable prognosis for long-lasting disability (6).

Instrumental Prognostic Investigations

Electrophysiologic techniques (EEG and evoked potentials [EP]) carry out an important role in the management of severe brain injury patients and should be integrated with neuroimaging techniques (computed tomography [CT] and MRI).

**Electroencephalogram**

An electroencephalogram (EEG) reactivity seems to be a very significant parameter, being minimally influenced by mild sedation (123,124). The presence of alpha-com, theta-com, triphasic waves, and spontaneous not reagent burst suppression are considered signs of an unfavorable outcome both in terms of survival and in quality of life (125). A possible predictive index for posttraumatic coma and VS prognosis that has raised interest in the past few years is the pattern of sleep organization. EEG patterns similar to those of sleep have been considered good prognostic markers (126–130).

**Somatosensory Evoked Potentials**

The International Federation of Clinical Neurophysiology (IFCN) (131) published guidelines on the interpretation of somatosensory evoked potentials (SEP) believed to be highly reliable from the prognostic standpoint (132).

**Acoustic Evoked Potentials**

Absent or abnormal brainstem acoustic evoked potentials (BAEPs) are universally poor predictors; in fact, 98% of these patients die or will remain in VS (132). Conversely, a delayed P300 component, which is a cognitive response, was observed in all patients with LIS, all MCS patients, and in three of five patients in a VS (133), whereas the presence of N400 event-related evoked potentials were able to differentiate VS, near VS, and patients not in VS (134).

In general, BAEPs have a better predictive value in terms of predicting survival, whereas SEPs are able to better predict quality of outcome. Outcome can become extremely accurate (99%) when EP and EEG are combined (124).

**Computed Tomography**

The Marshall classification (135) is widely used in the acute phase of a comatose patient as a discriminant of cerebral edema, focal or diffuse damage, and severity of diffuse axonal injury (DAI). Whereas hemorrhagic axonal injury can be seen on computed tomography (CT) as multiple foci of high attenuation, nonhemorrhagic injury can be missed. In fact, CT is abnormal in less than half of all patients with DAI (136).

**Magnetic Resonance Imaging**

Magnetic resonance imaging (MRI) can predict recovery from posttraumatic VS when brainstem damage is present (137,138). Proton MRI spectroscopy can detect the amount of creatine, choline, myosin, and N-acetylaspartate (NAA) in a selected tissue volume (139). NAA can be assumed to be a marker of neuronal loss. Several investigators have found that a lower NAA-to-creatine ratio correlates with poorer outcome after TBI (140–148). More recent studies correlated spectroscopic MRI with histologic changes, severity of TBI and VS prediction (149–155). Functional MRI (fMRI) is currently being explored as a method to predict the recovery of consciousness in those VS patients who will evolve toward MCS (61,62).

**Single Photon Emission Computed Tomography**

Since MRI detects lesions missed by single photon emission computed tomography (SPECT) and vice versa, a combination of MRI and SPECT may enhance or correct a prognostic prediction (156,157). Experience in this field is accumulating as the technology becomes more widely available.

**Positron Emission Tomography**

The reduction of cerebral metabolism by positron emission tomography (PET) can be useful to diagnose the extent of DAI (158). Recent PET studies in VS patients indicated altered activity in a critical frontoparietal cortical network, the restoration of which can be linked to a recovery of consciousness (159).

**REHABILITATION PROTOCOL IN THE ACUTE PHASE**

The ICU hospital course of severe brain injury patients may last from a few days to several weeks, but rehabilitation should start as soon as possible. Besides the evolution of the primary injury, infections are the most common impediment to early rehabilita-

The comatose patient frequently shows a high proneness to infections, secondary to central immunodepression (10) or peripheral facilitating factors such as the presence of a central venous catheter, tracheostomy tube, bladder catheter, pressure decubitus, and resistant nosocomial infections (160).

The utility of a passive range of motion in the acute phase is confirmed by experimental studies in animals, where it was demonstrated that a satisfying articular and muscle tendinous motion of range of motion may be maintained in subjects after prolonged immobility, only if every joint is mobilized daily and for 2 hours (161). Similarly, prevention of muscle contractures or atrophy can be prevented by dynamic positioning splitting (120,162,163).

State-of-the-art prevention of bed rest contractures include the following:

a. Early mobilization of the limbs to avoid joint contractures and para-articular osseification, osteoporosis, and nonuse muscular atrophy
b. Venous thrombosis prophylaxis at the lower limbs by means of elastic compression and specific pharmacotherapy (subcutaneous low-dose heparin)
c. Early recovery of the sitting position to counteract extensor muscle spasms and limit the tonic labyrinthine reflex (163)
The stabilization of the medical conditions and vital functions represents a fundamental requisite for the patient’s transfer potential from the ICU to the intensive rehabilitation unit. Besides the obvious requirement for hemodynamic stability, a diagnostic/therapeutic protocol for severe brain injury patients scheduled for transfer to a rehabilitation unit should include the following:

- Cerebral CT or MRI to rule out late neurosurgical complications such as chronic hematoma, hygroma, and hydrocephalus (57,164).
- Tracheobronchoscopy to rule out tracheal stenosis or esophagotracheal fistula, even in the absence of obvious respiratory stridor (165–168).
- Properly functioning enteral tube feeding, or a percutaneous endoscopic gastrostomy (PEG), when tube feeding has to be continued for > 1 month.
- Complete fever workup in case of recurrent and persistent hyperpyrexia.
- Endocrinologic investigation of possible hypopituitarism (107,108).
- Echo Doppler of the lower limbs to rule out silent venous thrombosis secondary to the prolonged bed rest (169–171).
- Electromyography and electroneurography of the upper and lower limbs in case of early muscular atrophy to rule out critical illness polyneuropathy (CIP) (24,172) or compressive neuropathies, secondary to articular ankylosis, pathologic postures, and inadequate positioning.

### Postacute Rehabilitation

The first rehabilitation goal after discharge from the ICU is the gradual recovery of the sitting position, with monitoring of the cardiovascular parameters, prevention of arterial orthostatic hypotension, and facilitation of exercises to improve head and trunk control in assisted sitting and passive standing positions.

An early phoniatric evaluation investigates respiratory air space by means of fibro-laryngoscopy, whereas a speech therapist examines daily oromotor abilities and dysphagia (173), including an evaluation of deglutition initiative, cough reflex elicitation, and risk of pulmonary aspiration. The first oral meal of adequate consistency has to be assisted by a phoniatric therapist, who has a specific expertise in swallowing training, compensatory posturing of the head during deglutition, and suctioning techniques. Winstein (174) reported that approximately 25% of the head-injured adults admitted to a rehabilitation facility demonstrated swallowing or oral motor problems on admission. Ninety-four percent of this group ultimately became successful oral feeders within 3 months, associated with a concomitant improvement of cognitive functions, primitive oral motor reflexes, and neurogenic dysphagia.

Respiratory training includes thorax clapping, bronchial secretions suctioning, cough elicitation, and forced expiratory exercises. Gradual downsizing of the tracheostomy tube size to closure should be monitored by pulse oximetry. Complications and setbacks are frequent in this phase, often requiring transferring of the patient to a higher acuity ward for events such as:

- Recurrent acute respiratory failure
- Recurrent infections or severe hyperthermia
- Progressive tracheal stenosis or tracheoesophageal fistula

### Plastic surgery of sacral and pressure calcaneal ulcers
- Stabilization of limb fractures or early excision of periarticular ossification
- Hydrocephalus or malfunctioning ventriculoperitoneal/atrial shunting (37)
- Worsening of chronic posttraumatic hematomas or hygromas requiring emergency craniotomy or early cranioplasty, since the latter may determine some clinical improvement (175–178).
In conclusion, clinical experience in postacute rehabilitation suggests the importance of a global approach to the TBI patient and the need to involve the family in the rehabilitation treatment. Adequate exchange with the family by means of psychosocial interviews may, in fact, allow a better understanding of the patient's premorbid personality and social network.

**PHARMACOTHERAPY**

An adequate pharmacologic treatment during coma and its re-awakening phases may accelerate the recovery process and improve symptoms and emerging syndromes (68). Although agitated severe brain injury patients often need sedation in the ICU, traditional neuroleptics should be avoided in the acute phase because of severe side effects such as vigilance reduction, extrapyramidal effects, epileptogenesis, and impairment of neural plasticity (194). Agitation may be controlled with fewer side effects by antiepileptic drugs such as carbamazepine and valproic acid (195,196). Similarly, the beta-blocker propranolol at low dosage is the only drug that demonstrated a significant efficacy in agitated patients according to the Cochrane Review (197). Propranolol should also be used for the control of vegetative dysautonomic symptoms, especially tachycardia and tachypnea, arterial hypertension, and severe sweating, all signs of sympathetic nervous system hyperactivity and hyperfunction of basal metabolism up to 180% (198, 199).

Tricyclic antidepressant agents such as amitriptyline, even if its use is no longer recommended (194,200); they may also be useful in the presence of spastic laughing and crying, chronic pain, depressive mood, or food refusal in the awakening phase, as well as activating agents (201). Benzodiazepines such as diazepam may be used when severe spasticity compromises spontaneous motility. Unfortunately, benzodiazepines and other commonly used drugs in these patients—such as clonidine, phenobarbital, cortisone, and haloperidol—have all shown adverse effects when used in the ICU (194). Recently, the minor tranquilizer zolpidem has been reported as facilitating consciousness recovery in chronic VS and MVS patients (202). Zolpidem is a GABA-A-enhancing agent acting on omega receptors and is generally used for insomnia. Some antiepileptic drugs, such as oxcarbazepine, gabapentin, clonazepam, and more recently, pregabalin, may be used for the treatment of epilepsy, myoclonic jerks, tremor, hyperpathia or dysesthesia, agitation, and dystonia (oral trigus). Restlessness and agitation may also be treated by atypical neuroleptics, such as clozapine, risperidone, olanzapine, quetiapine, and in some cases buspirone (68,203). One agent, quetiapine, has the advantage of causing less iatrogenic parkinsonism and to be less epileptogenic than the other neuroleptics (204,205) in patients already at risk for secondary epilepsy and for increasing tolerance to passive range of motion. Antidepressant drugs such as tricyclics and serotonergic (SSRI), mixed serotonergic, and noradrenergic agents have been occasionally used and found effective for motor, neuropsychological, and psychological recovery of TBI patients (208-210). Drugs such as baclofen, tizanidine, and diazepam are often used as muscle relaxant agents or antispasticity drugs. Among them, disodium dantrolene has the advantage of having a less sedative effect. Another more recent alternative is the botulinum toxin, used as a local infiltration for patients with segmental spasticity (211,212), whereas the continuous intrathecal infusion of baclofen (ITB) (baclofen pump) is used for diffuse spasticity, contractures, pain, and dysautonomic syndrome (213,214)—sometimes with responsibility improvement after ITB (215). The most common side effects of ITB, even if rarely reported, include hypotonia, asthma, myasthenia, dizziness, drowsiness, disorientation, nausea, vomiting, urine retention, constipation, and more rarely, cardiorespiratory depression, seizures, and paralytic ileus (216-218). The latter complication should be suspected especially in cases of brainstem injury, because baclofen acts directly over vegetative nuclei but can be easily minimized by reducing the total daily dose of the drug (210,212).

Despite the widespread use of antiepileptic drugs for prevention of posttraumatic epilepsy (PTE) (219-221), controlled studies and international guidelines demonstrated the lack of efficacy and recommend against their prophylactic use (222–223). Interestingly, the use of prophylactic antiepileptic therapy seems to increase the risk of late PTE during the discontinuation of treatment (226). Myoclonic jerks may be successfully treated by pipecuronium, clonazepam, and more recently, by levetiracetam (227–229).

A survey of 127 neurosurgical clinics showed that penetrating injuries, intracranial hemorrhages, rise in ICP, and electroencephalographic (EEG) abnormalities were the most frequent reasons why antiepileptic prophylaxis was initiated in the neurological ICU (230–232). Since traditional antiepileptic drugs may further compromise brain edema (233), valproic acid should be used only when restless or agitated patients are present during the ICU hospital course or in the case of late PTE. As for the treatment of early PTE, phenytoin is one of the drugs of choice in the ICU. The first-choice drugs among the traditional antiepileptics for late PTE are carbamazepine and valproic acid, whereas among the new antiepileptics drugs lamotrigine, topiramate, gabapentin, and especially levetiracetam seem to have less detrimental effects on cognitive function (233,234).

Resilience is frequently associated with chronic pain in severe brain injury patients, and it may be secondary to the central hyperpathia (thalamic syndrome) or peripheral dysesthesias (critical illness polyneuropathy [CIP]). The new antiepileptic drugs such as lamotrigine, topiramate, gabapentin, and pregabalin may also be useful for the treatment of chronic pain and for increasing tolerance to passive range of motion. The use of isotropic agents may be useful for counteracting somnolence and the iatrogenic soporiferous state induced by antiepileptic agents. In particular, pipecuronium, a cyclic derivative of gamma-aminobutyric acid (GABA), has been used for its inhibitory action on the excitatory amino acids (235,236).

Among the drugs with activating action, L-dopa showed electroencephalographic and behavioral effects of awakening, counteracting the hypnogenic effect of 5-hydroxytryptophan (42,237-240). Newman et al. (241), as well, reported an improvement in cognitive functions including logical association after L-dopa and carbidopa. Amantadine and dopaminergic drugs may improve both parkinsonian features and consciousness recovery (242–245). Similarly, Weinberg et al. (246) obtained good results in the recovery of cognitive functions in
patients with sequelae of TBI after dopaminergic drugs were given. Other authors reported an interesting positive effect of L-dopa and bromocriptine on the motor and cognitive recovery of postcomatose patients (247–249).

Amantadine, which exerts a dopaminergic effect and an inhibitory action on excitatory amino acids, demonstrated a significant efficacy in the improvement of attention, psychomotor speed, mobility, vocalization, motivation, and agitation in severe TBI patients (245,250–254). Finally, methylphenidate has demonstrated some effects on attention deficits after TBI, with associated improvement on restlessness and agitation (235).

In summary, the sequential pharmacotherapeutic protocol of severe brain injury patients should include the treatment of vegetative dysautonomia by means of beta-blockers (199). The reduction of muscle tone and the improvement of the passive range of motion ultimately prevent joint ankylosis and tendon shortening (120,236). Preventive therapy for PAO includes etidronate and nonsteroid antiphlogistic agents, especially indomethacin given at the dosage of 75 mg daily together with gastric protection (257–261).

Psychomotor agitation significantly impairs the potential for neurorehabilitation, especially when associated with pain and antagonistic behavior. The drugs of choice for controlling agitation are propranolol (197), carbamazepine, and valproic acid, as well as new antiepileptic drugs such as oxcarbazepine and lamotrigine. When antiepileptics are not effective against agitation and restlessness, amantadine (251) and amitriptyline (200) may be useful. Quetiapine can be introduced during propofol discontinuation in the ICU or when aggressiveness and delirium persist for long periods of time (205). L-Dopa and dopaminergic drugs may enhance consciousness and verbal communication recovery, improving cognitive functions and Parkinsonian symptoms (39,42,262).

## APPENDIX

### Appendix 1

**Levels of Cognitive Functioning**

(Personal communication: Chris Hagen, Ph.D.; Denise Malkmus, MA; Patricia A. Durham, Mx, Rancho Los Amigos Hospital; www.calpoly.edu/~lklooste/levels.htm).

1. **No response**
   - Patient appears to be in a deep sleep and completely unresponsive to any stimuli.

2. **Generalized response**
   - Patient reacts inconsistently and nonpurposefully to stimuli. Responses are limited in nature and are often the same regardless of the stimulus presented. Responses may be physiologic, gross body movements, and vocalization. Responses are likely to be delayed. The earliest response is to deep pain.

3. **Localized response**
   - Patient reacts specifically but inconsistently to stimuli. Responses are directly related to the type of stimulus presented, as in turning the head toward a sound or focusing on an object presented. The patient may withdraw an extremity and vocalize when exposed to a painful stimulus. He or she may follow simple commands in an inconsistent, delayed manner, such as closing the eyes, squeezing, or extending an extremity. Once external stimuli are removed, the patient may be quiet. He or she may also show a vague awareness of self and body by responding to discomfort by pulling at nasogastric tube or catheter, or resisting restraints. The patient may show a bias toward responding to some persons, especially family and friends, but not to others.

4. **Confused-agitated**
   - Patient is in a heightened state of activity with severe impairment to process information. Behavior is frequently bizarre and nonpurposeful relative to the immediate environment. He or she does not discriminate among persons or objects and is unable to cooperate directly with treatment efforts. Verbalization is frequently incoherent or inappropriate to the environment. Confabulation and hostility may be present. Being unaware of present events, the patient lacks short-term recall and may be reacting to past events. He or she is unable to perform self-care activities without maximum assistance. If not motor-disabled, the patient may perform automatic motor activities such as sitting, reaching, and ambulating as part of the agitated state but not necessarily as a purposeful act or on request.

5. **Confused-inappropriate**
   - Patient appears alert and is able to respond to simple commands fairly consistently. However, with increased complexity of commands or lack of any external structure, responses are nonpurposeful, random, or at best, fragmented toward any desired goal. With structure, the patient may be able to converse on a social-automatic level for short periods of time. Verbalization is often inappropriate; confabulation may be triggered by present events. The patient can usually perform self-care activities with assistance and may accomplish feeding with supervision. If the patient is physically mobile, he or she may wander off, either randomly or with vague intention of “going home.”

6. **Confused-appropriate**
   - Patient shows goal-directed behavior, but is dependent on external input for direction. He or she follows simple directions consistently and shows carryover for learned tasks, e.g., self-care. Responses may be incorrect due to memory problems but are appropriate to the situation. Selective attention to tasks may be impaired, especially with difficult tasks and in unstructured settings, but patient is now functional for common daily activities.

7. **Automatic-appropriate**
   - Patient appears oriented and acts appropriately within hospital and home settings, and goes through a daily routine automatically but robotically, with minimal to absent confusion, and has shallow recall for what he or she has been doing. Patient is independent in self-care activities and supervised in home and community skills for safety. With structure, the patient is able to initiate tasks or social and recreation activities in which he or she now has interest. The patient’s judgment remains impaired.

8. **Purposeful-appropriate**
   - Patient is alert and oriented, able to recall and integrate past and recent events, and is aware of and responsive to his or her culture. Within the patient’s physical capabilities, he or she is independent in home and community skills. The patient’s social, emotional, and intellectual capacities may continue to be at a decreased level from baseline but functional within society.
SUMMARY

In the intensive care unit (ICU), the hospital course of severe brain injury patients may last from a few days to several weeks. The reasons for a more prolonged length of stay include the persistent need of vital functions support and the recurrence of infections or hyperperfusion of central or peripheral cause (15). Timing of when best to transfer the patient from the ICU to rehabilitation facilities often represents the most delicate phase of the history of the comatose patient. Many complications may be avoided by adequate nursing care and early rehabilitation approach in the ICU (161–163). Adequate nursing care including correct hygiene and early passive range of motion of severe brain injury patients may reduce the occurrence and severity of the early and late complications and facilitate the transfer from the ICU to rehabilitation.

Finally, a focused pharmacologic approach should focus on the possible adverse effects in selected cases and only by experienced clinicians. Since severe brain injury carries a great deal of social disability and cost for the society, randomized multicenter controlled studies on clinical and pharmacologic intervention efficacy should be encouraged.

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Chapter 15: ICU Discharge Criteria and Rehabilitation Potential for Severe Brain Injury Patients
