Manejo del traumatismo craneoencefálico agudo moderado y grave

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Todos los temas se actualizan a medida que se dispone de nueva evidencia y se completa nuestro proceso de revisión por pares .

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INTRODUCCIÓN Y DEFINICIONES

La lesión cerebral traumática (TBI, por sus siglas en inglés) es una de las principales causas de muerte y discapacidad. En 2013, hubo aproximadamente 2,5 millones de visitas al departamento de emergencias (ED), 282 000 hospitalizaciones y 56 000 muertes relacionadas con TBI en los Estados Unidos [1]. Muchos sobrevivientes viven con discapacidades significativas, lo que también genera una gran carga socioeconómica. En 2010, el impacto económico de TBI en los Estados Unidos se estimó en $ 76,5 mil millones en costos directos e indirectos [2,3]. Una TBI más grave conlleva un costo económico desproporcionadamente mayor.

La gravedad de la LCT se clasifica con mayor frecuencia mediante la escala de coma de Glasgow (GCS), evaluada después de la reanimación inicial y dentro de las 48 horas posteriores a la lesión (tabla 1) [4]. TBI grave se define por una puntuación de GCS <9 [5]. Anteriormente, una puntuación GCS de 9 a 12 se consideraba una lesión moderada y una puntuación GCS de 13 a 15 se consideraba una lesión leve [6]. Más recientemente, sin embargo, el reconocimiento de que más de un tercio de los pacientes con una puntuación GCS de 13 tienen lesiones intracraneales ha llevado a una reevaluación de esta clasificación, con puntuaciones GCS 9 a 13 consideradas lesiones moderadas y 14 a 15 consideradas leves [7- 10].

One of the major advances over the past two decades in the care of patients with severe head injury has been the development of standardized approaches that follow international and national guidelines [11-14]. The Brain Trauma Foundation (BTF) updated its guidelines for the management of severe TBI in 2016 [15]. The intent of these guidelines has been to use existing evidence to provide recommendations for management in order to lessen heterogeneity and improve patient outcomes. Unfortunately, the lack of randomized clinical trials addressing many aspects of care of the severe TBI patient has meant that the strength of supporting data for several treatment concepts is relatively weak. Despite this, there is evidence that treatment in centers with neurosurgical support, especially in neurointensive care units that operate based on guideline-driven protocols, is associated with better patient outcomes [16-23].

Patients with moderate or severe head injury frequently have other traumatic injuries to internal organs, lungs, limbs, or the spinal cord. These are discussed in separate topic reviews. (See "Initial management of trauma in adults" and "Initial management of moderate to severe hemorrhage in the adult trauma patient" and "Overview of inpatient management of the adult trauma patient".)

This topic discusses the management of acute moderate and severe TBI. While most pertinent to severe TBI, the principles of management below are also relevant to moderate TBI (sometimes referred to as "potentially severe" TBI) [7,8]. The epidemiology and pathophysiology of TBI, the management of mild TBI, acute spinal cord injury, and other aspects of care of the trauma patient are discussed separately:

- (See "Traumatic brain injury: Epidemiology, classification, and pathophysiology".)
- (See "Acute mild traumatic brain injury (concussion) in adults".)
- (See "Acute traumatic spinal cord injury".)
- (See "Skull fractures in adults".)

INITIAL EVALUATION AND TREATMENT

Prehospital — The primary goal of prehospital management for moderate and severe TBI is the prevention and treatment of hypotension and hypoxia, two systemic insults known to be major causes of secondary injury after TBI [24-29]. The injured brain is especially vulnerable to secondary insults in the first 24 hours. In a meta-analysis of clinical trials and population-based studies, hypoxia (PaO_2 <60 mmHg) and hypotension (systolic blood pressure [BP] <90 mmHg) were present in 50 and 30 percent of patients, respectively, and were each associated with a higher likelihood of a poor outcome: hypoxia (odds ratio [OR] 2.14); hypotension (OR 2.67) [25]. Even low-normal BP may be associated with poor outcomes. An analysis of 5057 patients with

TBI entered into a European trauma registry revealed that the odds of death tripled with an admission systolic BP <90 mmHg, doubled with a systolic BP <100 mmHg, and were 1.5 times greater with an admission systolic BP <120 mmHg, after controlling for potential confounders [30].

Changes in prehospital management that aim to normalize oxygenation and BP may be associated with improved outcomes [31-35]:

- **Prehospital airway management** – Prehospital endotracheal intubation is recommended in patients with TBI and a Glasgow Coma Scale (GCS) score <9, an inability to protect their airway, or an SpO_2 <90 percent despite the administration of supplemental oxygen [36]. Patients who are not intubated should receive supplemental oxygen as necessary to maintain an SpO_2 >90 to 93 percent.

  When intubation is indicated but adequate expertise is unavailable, or an attempt at intubation is unsuccessful, bag-mask ventilation should be performed in conjunction with basic airway-opening maneuvers or airway adjuncts.

  The benefit of prehospital intubation is uncertain, with studies finding conflicting results [37]. Large observational studies have not found a benefit [38] and in some cases found harm to be associated with prehospital intubation [39]. One analysis suggested that prehospital intubation performed by aeromedical crews (often more experienced in the management of critically ill patients than ground crews) was associated with better outcomes [40]. In a randomized trial of 312 patients with severe TBI transported by ground in Australia, prehospital rapid-sequence intubation by paramedics was associated with better functional outcome at six months compared with intubation in hospital (51 versus 39 percent of patients with favorable outcome on the extended Glasgow Outcome Scale [E-GOS]) [41].

  Thus, the following factors should be considered by emergency medical service (EMS) systems when developing protocols that address the use of prehospital intubation in patients with severe TBI [38]:

  - Appropriate hands-on training of prehospital providers in rapid-sequence intubation, along with ongoing maintenance of skills, is essential.

  - Both hypoventilation and hyperventilation should be avoided following intubation. Quantitative capnography may be useful in this situation.

- Hemodynamic instability may occur following rapid-sequence intubation, and immediate measures should be taken to correct hypotension prior to emergency department (ED) arrival.

- While patients with more severe injury and a lower GCS score are more likely to require intubation, the GCS should not be the sole factor in making decisions on prehospital intubation. Patients with a poor initial neurologic exam will often improve prior to ED arrival.

  Factors that may influence the decision to intubate by a trained provider include:

  - Low GCS
  - Poor chest rise despite the use of airway repositioning and basic adjuncts (oropharyngeal airway device, nasopharyngeal airway device, suctioning)
  - SpO_2 <90 to 93 percent despite the use of supplemental oxygen
  - Clinical signs of cerebral herniation (see 'Patients with impending cerebral herniation' below)
  - Evidence of aspiration
  - Long transport time

- The use of a supraglottic airway device may be lifesaving when intubation is indicated but cannot be performed. (See "Extraglottic devices for emergency airway management in adults", section on 'Supraglottic airways'.)

- **Blood pressure management** – Prevention of hypotension in the prehospital setting is best accomplished by adequate fluid resuscitation using isotonic crystalloids. While hypertonic saline has theoretical benefits, including the need for a lower volume to achieve intravascular filling in patients with ongoing blood loss, randomized controlled trials in the prehospital setting have not suggested benefit [42,43].

- **Neurologic assessment** – Patients with TBI should be assumed to have a spinal fracture and appropriate precautions taken to stabilize and immobilize the spine during transport. (See "Acute traumatic spinal cord injury".)

  A prehospital assessment of the GCS can be helpful for early triage decisions (table 1).

- **Prehospital antifibrinolytic therapy** – We do not recommend the prehospital administration of antifibrinolytic therapy. In a randomized trial of 966 patients with TBI and GCS score ≤12, prehospital administration of tranexamic acid within two hours of injury did not improve mortality or six-month neurologic outcome [44].

Emergency department

Assessment and initial support — In the early hospital admission phase of patients with moderate or severe head injury, treatment and diagnostic assessment are performed according to the Advanced Trauma Life Support (ATLS) protocol. Important considerations specific to TBI include:

- Endotracheal intubation should be performed at this time for all patients with a GCS score <9, inability to protect the airway, inability to maintain SpO_2 >90 percent despite the use of supplemental oxygen, or clinical signs of cerebral herniation. Adequate oxygenation (PaO_2 >60 mmHg) continues to be a priority. Specific aspects of this procedure in this setting are described separately. (See "Airway management in the patient with elevated ICP for emergency medicine and critical care".)

- Vital signs including heart rate, BP, respiratory status (pulse oximetry, capnography), and temperature require ongoing monitoring. Hypoxia, hypoventilation, hyperventilation, and hypotension are scrupulously avoided [24].

- The patient should be assessed for other systemic trauma, per the ATLS algorithm. (See "Initial management of trauma in adults".)

- A neurologic examination should be completed as soon as possible to determine the clinical severity of the TBI. The GCS is commonly used to assess and communicate neurologic status in this setting (table 1). The pupillary examination is crucial in the patient with TBI.

  The Full Outline of UnResponsiveness (FOUR) score is an alternative scale for the assessment of patients with TBI (table 2) [45]. Potential advantages over the GCS include the ability to grade injury in intubated patients and to assess brainstem function. Prospective comparisons with the GCS in TBI have suggested an equivalent ability to predict long-term outcomes [46,47].

  Neurologic status should be frequently assessed. Deterioration is common in the initial hours after the injury. Interruption of sedative infusions may be required to obtain an examination that best reflects the actual neurologic status of the patient.

- Evaluation and management of increased intracranial pressure (ICP) should begin in the ED. Immediate lifesaving measures must be instituted in patients demonstrating clinical signs of impending or ongoing cerebral herniation [48]. These signs include significant pupillary asymmetry, unilateral or bilateral fixed and dilated pupils, decorticate or decerebrate posturing, respiratory depression, and the "Cushing triad" of hypertension, bradycardia, and irregular respiration. Patients who fulfill criteria may undergo placement of an ICP monitor in the ED. (See 'Initial (baseline) treatment' below and 'Patients with impending cerebral herniation' below and 'ICP and CPP monitoring' below.)

- A complete blood count, electrolytes, glucose, coagulation parameters, blood alcohol level, and urine toxicology should be checked. Efforts to reverse a coagulopathy should begin immediately. (See 'Management of coagulopathy' below.)

Patients with TBI should be transferred to a hospital with neurosurgical services as soon as they are hemodynamically stable [16-20].

Antifibrinolytic therapy — We recommend immediate administration of the antifibrinolytic tranexamic acid to patients who present to hospital with moderate TBI (GCS greater than 8 and less than 13) within three hours of injury. Treatment appears to be safe and is associated with decreased mortality.

Administration of tranexamic acid in the ED to other patients with TBI may also be reasonable. Examples include those with severe TBI but with bilateral reactive pupils, and patients with mild TBI (GCS >12) and evidence of intracranial bleeding. However, a benefit is uncertain in these patients.

Tranexamic acid 1 g is infused over 10 minutes, followed by an intravenous (IV) infusion of 1 g over eight hours.

A benefit for tranexamic acid in patients with moderate TBI was demonstrated in the CRASH-3 trial that randomized 9202 TBI patients with GCS score <13 or any evidence of intracranial bleeding on computed tomography (CT) scan within three hours of injury to tranexamic acid or placebo [49]. Overall, the risk of head injury-related death was nonsignificantly lower in the tranexamic acid group (18.5 versus 19.8 percent, relative risk (RR) 0.94, 95% CI 0.86-1.02); this difference was statistically significant when patients with unreactive pupils (bi- or unilateral) were excluded (11.5 versus 13.2 percent, RR 0.87, 95% CI 0.77-0.98). Among patients with mild to moderate TBI, death was significantly reduced (5.8 versus 7.5 percent, RR 0.78, 95% CI 0.64-0.95), but not in patients with severe TBI (RR 0.99, 95% CI 0.91-1.07). The benefit of tranexamic acid was highly time dependent in patients with mild to moderate injury, but not in patients with severe injury. Vaso-occlusive events were not increased in patients who received

tranexamic acid (1.5 versus 1.3 percent). Other smaller clinical trials have demonstrated the safety of tranexamic acid in TBI but individually did not demonstrate a benefit [50-52]. A meta-analysis of these data along with CRASH-3 does suggest a modest mortality benefit in TBI and supports our recommendation for tranexamic acid within three hours of injury in patients with moderate TBI. While benefit may also be present in patients with severe TBI and bilateral reactive pupils, as well as in those with mild injury and evidence of intracranial bleeding on CT, the impact on mortality is uncertain in these groups.

Mechanisms underlying the coagulopathy associated with trauma and the role of tranexamic acid in other acute traumatic injuries are discussed separately. (See "Coagulopathy in trauma patients".)

Neuroimaging — CT is the preferred imaging modality in the acute phase of head trauma and should be performed as quickly as possible in patients with moderate as well as severe TBI, as certain lesions will indicate potentially lifesaving neurosurgical interventions. (See 'Surgical treatment' below.)

A noncontrast CT scan will detect skull fractures, intracranial hematomas, and cerebral edema (image 1A-D). As these occur in patients with both moderate and severe TBI, guidelines recommend urgent head CT in all TBI patients with a GCS score of 14 or lower (table 1).

Follow-up CT scanning should be performed if there is any clinical deterioration. (See 'Neurologic monitoring' below.)

Screening for blunt cerebrovascular injury — Injury to the carotid and vertebral arteries most commonly occurs as a result of skull base or vertebral fractures that involve vulnerable segments of these vessels. While blunt cerebrovascular injury (BCVI) may result in stroke at the time of injury, a latency of several hours to several days between the trauma and cerebrovascular event is common. Because antithrombotic therapy during this latent period may prevent subsequent ischemic strokes, BCVI is important to identify.

We use the expanded Denver criteria to identify patients at high risk for BCVI, and perform multislice CT angiography of the head and neck to screen for such injury (algorithm 1). In patients with moderate or severe TBI who have BCVI, we typically initiate aspirin 81 mg daily when such injury is discovered and if no contraindications exist; anticoagulation with heparin is typically contraindicated in the setting of acute moderate or severe TBI. Other aspects of treatment and monitoring of carotid or vertebral artery injury with or without ischemic stroke are discussed separately. (See "Blunt cerebrovascular injury: Mechanisms, screening, and diagnostic evaluation" and "Blunt cerebrovascular injury: Treatment and outcomes".)

SURGICAL TREATMENT

Indications for emergency surgery after moderate or severe head injury are based upon neurologic status, usually defined by the Glasgow Coma Scale (GCS) (table 1), and findings on head CT criteria such as large hematoma volume or thickness and evidence of mass effect including midline shift (image 1A):

- **Epidural hematoma** – Surgical guidelines recommend evacuation of an epidural hematoma (EDH) (image 1D) larger than 30 mL in volume regardless of a patient's GCS score; emergency surgical evacuation is recommended for patients with acute EDH and coma (GCS score ≤8) who have pupillary abnormalities (anisocoria) [53]. (See "Intracranial epidural hematoma in adults", section on 'Management'.)

- **Subdural hematoma** – Acute subdural hematomas (SDHs) >10 mm in thickness or associated with midline shift >5 mm on CT should be surgically evacuated, regardless of the patient's GCS score (image 1A) [54]. In addition, surgery is recommended for patients with a GCS score ≤8 if the GCS score has decreased by ≥2 points from the time of injury to hospital admission, and/or if the patient presented with asymmetric or fixed and dilated pupils, and/or if intracranial pressure (ICP) measurements are consistently >20 mmHg.

- **Intracerebral hemorrhage** – Surgical evacuation of a traumatic intracerebral hemorrhage (ICH) in the posterior fossa is recommended when there is evidence of significant mass effect (brainstem compression, obliteration of the fourth ventricle, effacement of the basal cisterns, or obstructive hydrocephalus) [55].

  For traumatic ICH involving the cerebral hemispheres (image 1C), surgical indications are not as clearly defined. Consensus surgical guidelines recommend craniotomy with evacuation if the hemorrhage exceeds 50 cm^3 in volume, or if the GCS score is 6 to 8 in a patient with a frontal or temporal hemorrhage greater than 20 cm^3 with midline shift of at least 5 mm and/or cisternal compression on CT scan [56].

- **Penetrating injury** – Superficial debridement and dural closure to prevent cerebrospinal fluid (CSF) leak is generally recommended [57]. Small entry wounds can be treated with simple closure. Aggressive debridement and removal of deep foreign bodies such as bone or bullet fragments have not been shown to be effective in preventing delayed infection. The use of prophylactic broad-spectrum antibiotics is routine in this setting and is believed to have contributed to the reduced incidence of infection [58]. (See "Skull fractures in adults", section on 'Penetrating injuries'.)

- **Depressed skull fracture** – Elevation and debridement are recommended for open skull fractures depressed greater than the thickness of the cranium or if there is dural penetration, significant intracranial hematoma, frontal sinus involvement, cosmetic deformity, wound infection or contamination, or pneumocephalus [59]. (See "Skull fractures in adults", section on 'Depressed fractures' and "Skull fractures in children: Clinical manifestations, diagnosis, and management".)

- **Refractory intracranial hypertension** – Decompressive craniectomy may be lifesaving in patients with refractory elevations of ICP. (See 'Decompressive craniectomy' below.)

INTENSIVE CARE MANAGEMENT

A principal focus of critical care management for moderate or severe TBI is to limit secondary brain injury. In general, treatment efforts are aimed at intracranial pressure (ICP) management and maintenance of cerebral perfusion, as well as optimizing oxygenation and blood pressure (BP) and managing temperature, glucose, seizures, and other potential secondary brain insults.

Other aspects of the general medical care of the trauma patient are discussed in detail separately. (See "Overview of inpatient management of the adult trauma patient".)

Other extracranial traumatic injuries are managed simultaneously. (See appropriate topic reviews.)

Neurologic monitoring — A focus of management in moderate to severe TBI is the early recognition of neurologic worsening and the prevention of secondary brain injury. Of great concern, particularly in patients with moderate TBI, is neurologic worsening associated with expansion of hematoma or worsening cerebral edema, sometimes referred to as the "talk and die" phenomenon [60,61]. While the exact frequency of this phenomenon in moderate TBI is uncertain, a rule of thumb described by some authors is that approximately 30 percent of patients with moderate TBI will develop neurologic worsening and expansion of mass lesions [7,8].

Serial neurologic examinations performed every 1 to 2 hours for at least 24 to 48 hours is critical in patients with moderate TBI since ICP monitoring is not typically performed in this population. (See 'ICP and CPP monitoring' below.)

Urgent repeat imaging should be performed for any neurologic worsening. Evolution of CT findings is common and may indicate an alternative treatment approach in a significant number of patients [62-66]. While there is no clear indication for routine follow-up CT scans in

the absence of clinical change or changes in physiologic parameters such as ICP, practice varies considerably in this regard [67,68]. In the absence of clinical deterioration, repeat imaging in six hours is reasonable in patients with a hematoma present on the initial scan, particularly in patients with a Glasgow Coma Scale (GCS) score <9 [69]. Although contrast is not typically used, parenchymal contrast extravasation, as with spontaneous intracerebral hemorrhage (ICH), may predict a higher risk of hemorrhage progression [70]. (See "Spontaneous intracerebral hemorrhage: Pathogenesis, clinical features, and diagnosis", section on 'Predicting hemorrhage expansion'.)

Hemodynamic management

- **Fluids** – Isotonic fluids (normal saline) should be used to maintain euvolemia. Saline may be preferable to albumin; the latter was associated with increased mortality (42 versus 22 percent, p <0.001) in a post hoc analysis of patients with TBI enrolled in the SAFE clinical trial, which compared saline with albumin for fluid resuscitation in the intensive care unit (ICU) [71].

  While balanced crystalloid solutions (eg, lactated Ringer's and plasmalyte) are used to decrease the risk of acute kidney injury in other critically ill patients, normal saline is preferred in TBI, since balanced solutions are relatively hypotonic and may worsen cerebral edema. In the SMART ICU trial comparing saline with balanced solutions in the critically ill, exclusion of patients with TBI was permitted [72]. Among the TBI patients enrolled in SMART ICU, no benefit was seen with the use of balanced fluids. Electrolyte imbalances are common in patients with TBI and should be regularly assessed along with other laboratory parameters.

- **Blood pressure** – The avoidance of hypotension remains a priority in the ICU. Guidelines recommend maintaining the systolic BP ≥100 mmHg for patients 50 to 69 years old and ≥110 mmHg for patients 15 to 49 or >70 years old [15].

- **Cerebral perfusion pressure** – Through autoregulation, the normal cerebral vasculature maintains an adequate cerebral blood flow (CBF) across a wide range (50 to 150 mmHg) of mean arterial pressure (MAP). Cerebral autoregulation is disrupted in approximately one-third of patients with severe TBI [73-75]. In these patients, a rise in MAP can lead to elevated ICP due to increased cerebral blood volume and hyperemia, while drops in MAP may be associated with hypoperfusion and ischemia. Patients with impaired cerebral autoregulation are described as "pressure passive."

  While optimization of CBF is a foundation of TBI treatment, bedside measurement of CBF is not easily obtained. Cerebral perfusion pressure (CPP), the difference between the MAP

and the ICP (CPP = MAP – ICP), is a useful surrogate. Episodes of hypotension (low MAP), raised ICP, and/or low CPP are associated with secondary brain injury and worse clinical outcomes [31,32,76].

A goal CPP of 60 to 70 mmHg is recommended to improve survival and favorable outcomes [15]. Targeting a goal CPP >70 mmHg appeared to reduce mortality and morbidity in some earlier studies [77,78]. However, subsequent studies have suggested that routine use of this strategy does not improve outcomes and may increase the risk of acute hypoxic respiratory failure [78-80].

Efforts to optimize CPP should first focus on treatment of ICP elevation [81]. Patients with more severely impaired autoregulation and suboptimal CPP are best managed with efforts to lower ICP, rather than by elevating MAP with vasopressors; hypertension is more likely to worsen cerebral edema when protective autoregulation is impaired [79]. (See 'Intracranial pressure management' below.)

Continuous monitoring of cerebral oximetry or the pressure reactivity index (PRx) may help determine the adequacy of autoregulation and identify the optimal CPP in individual patients. (See 'Advanced neuromonitoring' below.)

Ventilation — Most patients with severe TBI are sedated and artificially ventilated during the first several days [82]. Since acute hypercarbia may result in elevations in ICP, and hypocarbia may precipitate cerebral ischemia, the use of end-tidal carbon dioxide ($ETCO_2$) monitoring should be considered for all ventilated TBI patients. Hypoxia should also be avoided, and the PaO_2 maintained >60 mmHg [24].

While hyperventilation can be used to reduce ICP, guidelines recommend avoiding hyperventilation because of safety concerns, especially in the acute phase (the first 24 to 48 hours) following TBI. Mild to moderate hyperventilation can be considered at later stages, but $PaCO_2$ of less than 30 mmHg should be avoided, except as a temporary intervention to help resolve ICP crises [83]. (See 'Patients with impending cerebral herniation' below.)

With hyperventilation, $PaCO_2$ decreases, leading to cerebral vasoconstriction, which then results in decreased cerebral blood volume and ICP. However, hyperventilation-induced vasoconstriction may also cause secondary ischemia and may thereby worsen outcomes [84-86]. Hyperventilation can also increase extracellular lactate and glutamate levels that may contribute to secondary brain injury [87]. In one randomized study, patients hyperventilated to a $PaCO_2$ of 25 mmHg for five days had a worse clinical outcome than nonhyperventilated controls [88]. The use of multimodality monitoring of cerebral oxygenation and metabolism

should also be considered when using therapeutic hyperventilation, to monitor its effects and prevent ischemic episodes [85,86,89]. (See 'Advanced neuromonitoring' below.)

While patients with TBI frequently suffer acute hypoxic respiratory failure and require higher levels of positive end-expiratory pressure (PEEP), a theoretical concern has been that elevated intrathoracic pressures will hamper venous return from the brain and worsen ICP. Studies of applied PEEP up to 15 to 20 cm H_2O [90-92], as well as ventilator modes such as airway pressure release ventilation (APRV) [93], have not revealed a consistent effect on ICP, although patients with severe lung injury did demonstrate a small but statistically significant positive relationship between PEEP and ICP (0.31 mmHg rise in ICP for every 1 cm H_2O rise in PEEP) in one retrospective study [90]. The use of PEEP in TBI patients with acute respiratory distress syndrome (ARDS) does, however, seem to significantly improve brain tissue oxygenation [92]. Our practice, therefore, is to use PEEP up to 15 to 20 cm H_2O, as well as APRV when clinically appropriate, for the management of ARDS in patients with TBI in conjunction with monitoring of ICP.

Antiseizure medications and electroencephalography monitoring — Antiseizure medications are generally recommended to prevent and treat post-traumatic seizures in patients with TBI and any of the following: cortical contusion visible on CT scanning; a subdural, epidural, or intracerebral hematoma; a depressed skull fracture; a penetrating head wound; a seizure within 24 hours of injury; or a GCS score <11 [94,95]. We typically use levetiracetam [96]. Patients with TBI who develop any seizures will require ongoing antiseizure therapy. The duration of antiseizure medication therapy in severe TBI patients who do suffer seizures is not well established; this is discussed separately. (See "Posttraumatic seizures and epilepsy", section on 'Management of early seizures'.)

- **Indications for treatment and monitoring** – The incidence of early post-traumatic seizures (within the first week or two) may be as high as 30 percent in patients with severe TBI [97-99]. In addition, case series suggest that approximately 15 to 25 percent of patients with coma and severe head injury will have nonconvulsive seizures identified on continuous monitoring with electroencephalography (EEG) [99-101]. While the clinical significance of clinically silent electrographic seizures is unclear, we monitor patients with EEG if there is persistent impaired consciousness that is disproportionate to the extent of injury visible on imaging. We generally continue antiseizure medications if there are electrographic seizures. The assessment and treatment of nonconvulsive status epilepticus are discussed separately. (See "Nonconvulsive status epilepticus: Treatment and prognosis".)

The use of antiseizure medications in the acute management of TBI has been shown to reduce the incidence of early seizures but does not prevent the later development of epilepsy [94,95]. In one trial of 404 patients with TBI and high seizure risk (ie, cortical contusion, intracranial hemorrhage, depressed skull fracture, penetrating injury, seizure within 24 hours, or GCS score <11), phenytoin reduced the risk of seizures within the first week (3.6 versus 14.2 percent) [94]. However, there was no reduction in the incidence of seizures at any subsequent time points up to two years after injury, and no difference in mortality.

Reasons to prevent early seizures include the risk of status epilepticus, which has a high fatality rate in this setting, and the potential of convulsions to aggravate a systemic injury [99]. In addition, recurrent seizures may increase CBF and could thereby increase ICP. Another potential concern is that seizures place a metabolic demand on damaged brain tissue and may aggravate secondary brain injury.

- **Choice of antiseizure medication** – While certain guidelines recommend phenytoin to prevent early post-traumatic seizures for the first seven days following injury [15], we prefer levetiracetam in this setting.

  Studies of phenytoin use in other conditions such as subarachnoid hemorrhage have revealed an adverse association between higher cumulative dosing of phenytoin and worse long-term functional and cognitive outcomes [102]. A randomized clinical trial that compared levetiracetam with phenytoin for seizure prophylaxis in neurosurgical ICU patients (89 percent with TBI) revealed equivalent efficacy for seizure prevention but improved six-month functional outcomes with levetiracetam [96]. A subsequent single-center randomized clinical trial did not demonstrate a reduction in inpatient adverse events with levetiracetam compared with phenytoin, but did not assess long-term functional outcomes [103]. A subsequent meta-analysis that included observational studies revealed fewer adverse drug events with levetiracetam [104].

Post-traumatic seizures and epilepsy are discussed in detail separately. (See "Posttraumatic seizures and epilepsy".)

Venous thromboembolism prophylaxis — Patients with TBI are at increased risk of venous thromboembolism (VTE). We initiate mechanical prophylaxis with intermittent pneumatic compression on admission for all patients with TBI, and chemoprophylaxis with either unfractionated heparin 5000 units three times daily or with enoxaparin 40 mg daily 24 hours following admission in most TBI patients with stability confirmed on repeat imaging.

The efficacy and safety of mechanical thromboprophylaxis using intermittent pneumatic compression is discussed separately [105,106]. (See "Prevention of venous thromboembolic disease in adult nonorthopedic surgical patients".)

While VTE risk can be further reduced with antithrombotic therapy, this has to be weighed against the potential risk of hemorrhage expansion, which is greatest in the first 24 to 48 hours [107-109]. Data examining this trade-off in patients with severe TBI are limited. While some observational studies suggest that antithrombotic therapy may not be associated with increased risk of intracranial hemorrhage expansion [110-112], others have found a higher rate of hemorrhage progression with the use of low molecular weight heparin [113]. One pilot study randomly assigned 62 patients with low-risk TBI to enoxaparin or placebo [114]. Subclinical, radiographic progression of intracranial hemorrhage was nonsignificantly more common in the treated patient group; no patient suffered a clinical progression; one patient in the placebo group developed deep vein thrombosis (DVT). A more recent meta-analysis of clinical trials and observational studies concluded that the use of pharmacologic VTE prophylaxis was safe when initiated within 24 to 48 hours of injury in TBI patients with stability demonstrated on repeat imaging [115]. (See "Prevention of venous thromboembolic disease in adult nonorthopedic surgical patients".)

Management of coagulopathy — Coagulation parameters should be measured in the emergency department (ED) in all patients with moderate or severe TBI, and efforts to correct any identified coagulopathy should begin immediately.

Approximately one-third of patients with moderate or severe TBI demonstrate a coagulopathy, which is associated with an increased risk of hemorrhage enlargement, poor neurologic outcomes, and death [116-121]. The coagulopathy may result from existing patient medications such as warfarin or antiplatelet agents. Acute TBI is also thought to produce a more subtle coagulopathy through the systemic release of tissue factor and brain phospholipids into the circulation leading to inappropriate intravascular coagulation and a consumptive coagulopathy [121-123].

- Patients taking warfarin may be managed with prothrombin complex concentrate (PCC) and vitamin K as recommended for patients with warfarin-associated ICH. (See "Reversal of anticoagulation in intracranial hemorrhage".)

  Reversal of direct oral anticoagulants is discussed separately. (See "Management of bleeding in patients receiving direct oral anticoagulants", section on 'Major bleeding'.)

- In patients with thrombocytopenia, some centers choose to maintain a platelet count >75,000/microL with platelet transfusions if necessary. In one cohort analysis, a platelet

count of <135,000/microL was associated with a 12.4 times higher risk of hemorrhage expansion, while a platelet count of <95,000/microL identified patients who were 31.5 times more likely to require neurosurgical intervention [124]. There is insufficient evidence at this time to support the routine use of a specific goal platelet count.

The utility of platelet transfusions in TBI patients who arrive on antiplatelet medications is not known, although the incidence of neurologic worsening is greater in such patients [124,125]. (See "Use of blood products in the critically ill", section on 'Platelets'.)

Recommendations for coagulation reversal in other categories of patients with moderate or severe TBI are limited by lack of evidence [126]. When a coagulopathy is identified, it is reasonable to use fresh frozen plasma (FFP), PCC, and/or vitamin K as for warfarin reversal. A reasonable, if somewhat arbitrary, target is an international normalized ratio (INR) <1.4. A phase II dose-escalation clinical trial of recombinant factor VIIa in TBI patients demonstrated a nonsignificant trend towards limiting hematoma expansion but no mortality benefit, although this was not directed exclusively at patients with TBI-related INR elevation [127].

Recombinant human factor VIIa has not been shown to be of overall benefit in patients with nontraumatic ICH and is not used in the setting of traumatic ICH. (See "Spontaneous intracerebral hemorrhage: Acute treatment and prognosis", section on 'Reverse anticoagulation'.)

Glucose management — Avoidance of both hypo- and hyperglycemia is appropriate in patients with moderate or severe TBI, but further studies are needed to clarify the optimal serum glucose target range and duration of therapy. To avoid extremes of very high or low blood glucose levels, we target a range of 140 to 180 mg/dL. (See "Glycemic control in critically ill adult and pediatric patients".)

Both hyper- and hypoglycemia are associated with worsened outcome in a variety of neurologic conditions including severe TBI [128-130]. This has been presumed to be at least in part related to aggravation of secondary brain injury. Several mechanisms for this are proposed, including increased tissue acidosis from anaerobic metabolism, free radical generation, and increased blood-brain barrier permeability.

We do not use intensive insulin therapy to target a glucose level between 80 to 110 mg/dL. One case series using cerebral microdialysis found that tight glycemic control was associated with reduced cerebral glucose availability and elevated lactate:pyruvate ratio, which in turn was associated with increased mortality [131]. Moreover, this approach is associated with a greater risk of hypoglycemia and worse outcomes in other critically ill patients. (See "Glycemic control in critically ill adult and pediatric patients".)

Temperature management — Fever should be avoided. Fever is associated with worse outcome after stroke and probably severe head injury, presumably by aggravating secondary brain injury [31]. Fever also worsens ICP control through an increase in metabolic demand, blood flow, and blood volume.

Maintenance of normothermia should be attempted with the use of antipyretic medications, surface-cooling devices, or endovascular temperature management catheters. While induced normothermia using endovascular cooling and a continuous feedback-loop system has been shown to lower the fever burden and improve ICP control following TBI [132], this approach has not been systematically tested with regard to clinical outcome. Our preference is to use surface cooling with adhesive pads and continuous feedback-loop regulation to maintain normothermia in patients with severe TBI and elevated ICP.

Shivering may complicate these treatments and can increase metabolic demand and worsen brain tissue oxygenation [133]. The management of shivering is discussed separately. (See "Intensive care unit management of the intubated post-cardiac arrest adult patient", section on 'Adverse effects'.)

Noninduced hypothermia has been associated with an increase in mortality after TBI [134], but the efficacy of efforts to avoid this complication has not been evaluated.

The role of therapeutic induced hypothermia is discussed separately. (See 'Hypothermia' below.)

Paroxysmal sympathetic hyperactivity — Occurring in approximately 10 percent of patients with severe TBI, paroxysmal sympathetic hyperactivity (PSH) is characterized by episodes of hypertension, tachycardia, tachypnea, hyperthermia, diaphoresis, increased tone, and posturing of varying severity that are often but not always triggered by external stimuli.

Depending on the symptom complex, other conditions, such as pulmonary embolism, may need to be excluded. Appropriate management includes avoiding those stimuli that provoke attacks and a combination of abortive and preventive medications.

The diagnosis and management of PSH are discussed in detail separately. (See "Paroxysmal sympathetic hyperactivity".)

Nutritional support — Guidelines recommend that basic nutritional goals be attained no later than five to seven days from injury, and that transpyloric enteral nutrition be considered to decrease the rate of ventilator-associated pneumonia [15,135]. There is some evidence that early enteral nutrition may decrease rates of pneumonia [136] as well as mortality [137]

following TBI, although a randomized controlled trial did not demonstrate a reduction in complications [138]. (See "Nutrition support in critically ill patients: An overview".)

INTRACRANIAL PRESSURE MANAGEMENT

Elevated intracranial pressure (ICP) is associated with increased mortality and worse outcome [139-141].

Specific measures regarding ICP management in the setting of TBI are discussed here. The evaluation and management of elevated ICP in other settings are discussed in detail separately. (See "Evaluation and management of elevated intracranial pressure in adults".)

A tiered approach to management of elevated ICP in severe TBI is shown in the algorithm (algorithm 2).

Initial (baseline) treatment — Simple techniques should be instituted as soon as possible:

- Head of bed (HOB) elevation to 30° to permit adequate venous drainage from the brain while not compromising cerebral perfusion
- Optimization of venous drainage: keeping the neck in neutral position, loosening neck braces if too tight

Patients with impending cerebral herniation — All patients should be quickly assessed for impending cerebral herniation; such assessments are typically performed every one to two hours in the first few days after moderate or severe TBI. Clinical signs of impending herniation include significant pupillary asymmetry, unilateral or bilateral fixed and dilated pupils, decorticate or decerebrate posturing, respiratory depression, and the "Cushing triad" of hypertension, bradycardia, and irregular respiration. In such patients, the following measures must be taken immediately:

- Endotracheal intubation, if not already performed, keeping in mind the specific considerations outlined above. (See 'Emergency department' above.)
- Elevation of the HOB to 30 to 45°, with the head maintained in the neutral position, to permit adequate venous drainage from the brain while not compromising cerebral perfusion.
- Brief hyperventilation to a pCO_2 of approximately 30 mmHg (end-tidal carbon dioxide [$ETCO_2$] 25 to 30 mmHg), as a lifesaving measure. Hyperventilation will rapidly and reliably

lower the ICP in the setting of cerebral herniation [48]. However, prolonged use is potentially harmful and is not recommended. (See 'Ventilation' above.)

- Use of a bolus dose of an osmotic agent capable of transiently reversing cerebral herniation. The two agents that have demonstrated efficacy in published studies to acutely reverse herniation are:

  - Mannitol: 1 to 1.5 g/kg [142]

  - 23.4 percent sodium chloride (NaCl): 30 to 60 mL administered over 10 minutes [143]

  Since mannitol may result in volume depletion, we prefer 23.4 percent NaCl, particularly in trauma patients with ongoing blood loss, hemodynamic instability, or renal failure. Excessively rapid administration of 23.4 percent NaCl can, however, provoke transient but profound hypotension [143]. While the administration of 23.4 percent NaCl through central venous access is preferred, this agent may be administered safely via peripheral venous access in life-threatening situations such as impending or ongoing cerebral herniation and severe ICP elevation [144]. Guidelines recommend that mannitol use prior to the initiation of ICP monitoring be restricted to the management of cerebral herniation or acute neurologic deterioration that is not attributable to extracranial causes [15].

- Maintenance of a higher mean arterial pressure (MAP), to approximately 80 to 100 mmHg, to maintain an adequate cerebral perfusion pressure (CPP), since the ICP may be extremely high in the setting of cerebral herniation. Both fluid resuscitation and vasopressor use are frequently necessary in this setting.

Such interventions are a temporizing measure pending more definitive interventions, including neurosurgical treatment.

ICP and CPP monitoring — Current Brain Trauma Foundation (BTF) guidelines recommend that information from ICP monitoring be used to guide the management of patients with severe TBI (Glasgow Coma Scale [GCS] score <9) in order to reduce in-hospital and two-week postinjury mortality [15]. We recommend the use of ICP monitoring in patients with moderate TBI without a reliable neurologic examination because of prolonged sedation or anesthesia within the first 48 hours of injury, and in patients who suffer neurologic worsening to GCS score <9.

A ventricular catheter, also known as an external ventricular drain (EVD), connected to a strain gauge transducer is the most accurate and cost-effective method of ICP monitoring and has the therapeutic advantage of allowing for cerebrospinal fluid (CSF) drainage to treat rises in ICP

(figure 1) [145]. Intraparenchymal ICP monitors are technically easier to place and are associated with a lower risk of hemorrhage and infection than EVDs. An intraparenchymal catheter may be an acceptable alternative when the risk of bleeding or infection is thought to be higher than usual, or when EVD placement is unsuccessful because of technical difficulty. Significant midline shift and ventricular collapse ("slit ventricles") will increase the technical difficulty of EVD placement. Intraparenchymal catheters permit continuous monitoring of ICP, while most EVDs only permit measurement of ICP when the stopcock is closed to CSF drainage and open to the transducer. Intraparenchymal catheters may therefore be utilized in conjunction with an EVD when continuous CSF drainage is performed. Intraparenchymal catheters have been preferentially used for ICP monitoring of severe TBI patients in some resource-limited settings because of the perceived high baseline risk of infection [146,147]. However, low-cost techniques of external ventricular drainage for ICP monitoring are also recommended in these settings [148]. Other monitor types are discussed separately. (See "Evaluation and management of elevated intracranial pressure in adults", section on 'Types of monitors'.)

An ICP goal ≤22 mmHg is recommended as the threshold that predicts survival and favorable outcome following TBI [15,149]. Therapeutic measures are initiated in a stepwise manner to attain this goal, starting with CSF drainage, sedation, and analgesia as described in sections below.

ICP monitoring allows ongoing assessment of CPP, itself an approximation of the more clinically relevant cerebral blood flow (CBF). Targeting a goal CPP of 60 to 70 mmHg appears to reduce mortality and morbidity [15,77,78]. Efforts to optimize CPP should first focus on treatment of ICP elevations [81]. Patients with more severely impaired autoregulation and suboptimal CPP are best managed with efforts to lower ICP, rather than by elevating MAP with vasopressors; hypertension is more likely to worsen cerebral edema when protective autoregulation is impaired [79].

While ICP monitoring has long been central to the management of patients with severe head injury, the strength of this recommendation has been limited by the lack of large randomized trials examining the effect of ICP monitoring and treatment on outcome [150-152]. One randomized study of 324 patients older than 12 years with severe TBI hospitalized in Bolivia or Ecuador (BEST TRIP) found no differences in outcomes among those patients assigned to management guided by invasive ICP monitoring consistent with guidelines versus patients assigned to a treatment protocol based on high-intensity clinical and imaging evaluation [146]. While this trial demonstrated the feasibility of managing patients in low-resource environments using frequent clinical and imaging evaluations, as an alternative to invasive ICP monitoring, its

findings are not considered to be generalizable to the management of severe TBI in other settings. Other important limitations of the trial include limited use of CSF drainage, multiple statistically significant differences in therapeutic measures between treatment arms that may have impacted outcomes, and limitations in the availability of rehabilitative services following discharge. By contrast, registry-based studies from New York and India [147,153] have demonstrated decreased in-hospital mortality with the use of invasive ICP monitoring to guide therapy, even after controlling for potential confounders.

Several noninvasive techniques of ICP monitoring have been evaluated [154]. Sonographic measurement of the optic nerve sheath diameter (ONSD) has shown promise in some studies [155-157]; however, prespecified thresholds of diagnostic accuracy were not met in a subsequent prospective study of 120 patients with severe TBI and concomitant invasive ICP monitoring evaluated with ONSD [158]. Transcranial Doppler has also been evaluated for noninvasive ICP assessment, with variable results [159-161]. All of these techniques are currently considered investigational and should not be used to direct clinical management.

Cerebrospinal fluid drainage — In patients with a ventricular catheter, drainage of CSF is generally the first intervention for lowering ICP. Drainage may be continuous or intermittent, with a limited volume of CSF drained in response to elevations in ICP above goal.

Based on observational data, guidelines recommend continuous CSF drainage for better control of ICP compared with intermittent drainage [15,162]. Continuous drainage is particularly recommended in patients with a GCS score <6 in the first 12 hours [15]. Caution must be utilized with continuous drainage, however, since excessive drainage can lead to ventricular collapse and malfunctioning or occlusion of the catheter in the setting of cerebral edema and small ventricles.

Sedation and analgesia — Protocol-based analgosedation is recommended by 2018 guidelines from the Society of Critical Care Medicine to decrease duration of mechanical ventilation and intensive care unit (ICU) length of stay [163]. Analgosedation may consist of either analgesia-first sedation or analgesia-based sedation. With analgesia-first sedation, an opioid such as fentanyl is used before, then often in conjunction with, a sedative infusion to achieve sedation goals. Analgesia-based sedation consists of the use of an opioid infusion alone, titrated to high enough doses to achieve a sedation goal without a concomitant sedative infusion. While either approach is a reasonable first step in the management of the intubated patient with severe TBI, patients with significant ICP elevation should be managed with an effective sedative agent in conjunction with the opioid infusion. Appropriate analgesia and sedation may lower ICP by reducing cerebral metabolic demand, and thereby CBF and cerebral blood volume [164].

Sedation may also ameliorate ventilator asynchrony and blunt sympathetic responses of hypertension and tachycardia.

Effective analgesia is a critical first step, since patients with TBI often have pain that goes unrecognized. Fentanyl infusions are commonly used in this setting for greater efficacy compared with morphine, and to minimize hemodynamic instability. (See "Pain control in the critically ill adult patient".)

Propofol may be the preferred sedating agent in this setting because of its efficacy in decreasing cerebral metabolic demand and ICP, as well as its short duration of action that allows intermittent clinical neurologic assessment [165]. In one trial, propofol appeared to be associated with better ICP control and a trend toward better outcomes compared with morphine alone [166]. Propofol also has putative neuroprotective effects [167]. Hypotension is common with propofol, and fluids and vasopressors should be used as appropriate to maintain CPP goals. The propofol infusion syndrome (severe metabolic acidosis, rhabdomyolysis, hyperkalemia, renal failure, and cardiovascular collapse) is a rare complication that is more likely to occur with the use of high rates of infusion over extended periods of time [168]. Other considerations in the selection of sedative agents in the critical care setting are discussed separately. (See "Sedative-analgesic medications in critically ill adults: Selection, initiation, maintenance, and withdrawal".)

In general, light sedation, to a goal Richmond Agitation-Sedation Scale (RASS) (table 3) of 0 to -2, is recommended when the ICP is adequately controlled [164]. Deeper levels of sedation, to a RASS of -4 to -5, are often necessary when ICP elevation is refractory to light sedation.

Dosing and administration of sedative and analgesic agents in the critical care setting is described in detail separately (table 4). (See "Sedative-analgesic medications in critically ill adults: Properties, dose regimens, and adverse effects".)

Neuromuscular blockade may decrease ICP elevations associated with ventilator dyssynchrony and coughing. However, the routine use of paralytic medications is discouraged, since these agents may result in prolonged neuromuscular weakness and delay weaning from mechanical ventilation. (See "Neuromuscular weakness related to critical illness".)

Osmotic therapy — Osmotic therapy (mannitol or hypertonic saline) is generally utilized in TBI patients who are clinically symptomatic from cerebral edema or have documented ICP elevation that does not respond to initial measures such as CSF drainage, analgesia, and sedation.

Intravascular injection of hyperosmolar agents (hypertonic saline, mannitol) creates an osmolar gradient, drawing water across the blood-brain barrier [169]. This leads to a decrease in brain

volume and a decrease in ICP.

Protocols — We use an infusion of 3 percent NaCl to achieve a sodium goal of 145 to 155 mEq/L in patients with elevated ICP. In addition, we use supplemental 30 mL bolus doses of 23.4 percent NaCl, administered over 10 minutes, to treat acute ICP elevations. Mannitol is an acceptable alternative. No specific hyperosmolar treatment protocol has been shown to improve function outcome or mortality in clinical trials.

The effect of hyperosmolar therapy diminishes with time, as a compensatory increase in brain osmoles occurs within 24 hours [170,171]. Thus, hyperosmolar agents should be weaned slowly after prolonged use to prevent a reversal in the osmotic gradient and consequent rebound cerebral edema.

- **Hypertonic** saline is an effective hyperosmolar agent for the control of elevated ICP [93,147,170,172-181]. This agent has been used in a wide range of concentrations, from 3 percent, most commonly used as a continuous infusion, to 23.4 percent, which is typically used in intermittent boluses [182,183]. When used as a continuous infusion, 3 percent NaCl may be titrated to an initial sodium goal of approximately 145 to 155 mEq/L. Hypertonic saline should be administered via a central venous catheter because of the risk of extravasation injury when used with peripheral intravenous (IV) access. Short-term use via peripheral IV access is permissible in the setting of acute ICP elevation, however, while central access is obtained.

  Hypertonic saline has several theoretical advantages over mannitol [170]. In particular, volume depletion and hypovolemia do not occur, which makes this agent safer in the trauma patient with ongoing blood loss, hypovolemia, or hypotension. Hypertonic saline has a reflection coefficient of 1.0 (compared with 0.9 for mannitol), and is therefore less likely to leak into brain tissue. Potential adverse effects include circulatory overload and pulmonary edema, and an increased chloride burden, which may result in a non-anion gap metabolic acidosis [184]. (See 'Monitoring and complications' below.)

- Mannitol has also been shown to reduce ICP and improve CBF [151,185-189]. Mannitol is administered in boluses of 0.25 to 1 g/kg every four to six hours as needed.

  A serious albeit theoretical concern with mannitol use is leakage into brain tissue in patients with disruption of the blood-brain barrier, with consequent reversal of the osmolar gradient and rebound cerebral edema [190,191]. Judicious administration of mannitol, on an as-needed basis for elevations in ICP, is advisable to minimize this potential risk. (See "Evaluation and management of elevated intracranial pressure in adults", section on 'Mannitol'.)

In the aggregate, multiple observational studies [177,180], small randomized clinical trials [172,173,178,181], meta-analyses [175,179], and systematic reviews [176] have not found compelling evidence to suggest superiority of either agent to improve outcomes such as mortality or functional recovery. The majority of studies do suggest improved ICP control with hypertonic saline [172,173,176-180], along with possible improvements in cerebral perfusion [178,180] and brain tissue oxygenation [180].

Monitoring and complications — Serial measurement of electrolytes, often at four- to six-hour intervals, is primarily performed for safety, to prevent excessive elevation of sodium and chloride levels, and to detect and correct other derangements such as hypokalemia. Ongoing fluid balance should also be closely monitored. Hypernatremia is associated with increased mortality in severe TBI [192]. This association may reflect an effect of diabetes insipidus (DI) [192], often a marker of more extensive brain injury that includes the hypothalamic-pituitary axis.

In addition, for patients receiving mannitol, serum osmolality should be monitored and maintained <320 mmol/L to minimize complications. Renal function tests are checked daily. As an osmotic diuretic, mannitol may cause dehydration and acute kidney injury. (See "Complications of mannitol therapy".)

Hypernatremia should be corrected gradually, if at all. Severe rebound cerebral edema may occur when the sodium level, and therefore serum osmolality, is lowered too quickly. There is no high-quality evidence for a specific upper limit of sodium that necessitates correction in this setting, and management should be individualized. Patients with renal failure may be at higher risk for complications from hyperchloremia [72]. Patients with DI should also be managed more aggressively, primarily to treat hypovolemia and the free water deficit. (See "Arginine vasopressin deficiency (central diabetes insipidus): Treatment".)

In the absence of these conditions and in the setting of elevated ICP or severe cerebral edema, we rarely correct a sodium level under 160 to 165 mEq/L. When the sodium level is lowered, we avoid correction by more than 5 mEq/L in a 24-hour period, and we closely monitor the patient's neurologic status and ICP. (See "Treatment of hypernatremia in adults".)

Refractory ICP elevation — Patients with elevated ICP that is refractory to the measures described above may be managed with decompressive craniectomy, barbiturate coma, or hypothermia.

Decompressive craniectomy — Decompressive craniectomy is effective in controlling ICP and is potentially lifesaving in patients who have failed medical therapy. Guidelines recommend the use of decompressive craniectomy in patients with severe TBI and ICP elevation above goal for

>1 to 12 hours despite the use of at least two tiers of medical therapy (late refractory ICP elevation) [193]. While many patients who require decompressive craniectomy as a lifesaving procedure will suffer severe disability, some survivors will attain a functional outcome of independence within the home or better.

In a decompressive craniectomy, a substantial portion of the skull is removed to allow brain tissue to swell beyond the confines of the cranial vault, which otherwise restricts the total volume contained within (the Monro-Kellie doctrine). A craniectomy of sufficient size can rapidly relieve intracranial hypertension. A "primary" or prophylactic craniectomy is performed in anticipation of elevated ICP, most often at the time of hematoma evacuation, or on the basis of clinical or imaging findings on presentation that suggest the presence of life-threatening intracranial hypertension [194,195]. A "secondary" or therapeutic decompressive craniectomy is performed to control proven ICP elevation (measured using invasive monitoring) that is refractory to medical therapy.

Attention to specific technical considerations is particularly important [194,195], since an ineffective decompression will expose the patient to the risks of the procedure without the anticipated benefit:

- The site and extent of bone removal should be tailored to the predominant location of injury and edema. A hemicraniectomy (removal of one side of the skull) is performed for predominantly unilateral injury, while a large bifrontal craniectomy, with variable extension into the temporal and parietal bones, is necessary for bifrontal or diffuse injury.

- The craniectomy must be of sufficient size. An insufficient skull defect may be ineffective in resolving intracranial hypertension, while causing additional injury when cortical veins are compressed against the edge of the skull defect, leading to venous infarction. Two randomized clinical trials have demonstrated a reduction in poor long-term functional outcome with the use of larger compared with more limited decompressive craniectomy [196,197]. Guidelines recommend a large frontotemporoparietal decompressive craniectomy (not less than 12 × 15 cm or 15 cm in diameter) over a smaller frontotemporoparietal craniectomy to decrease mortality and improve neurologic outcomes [193].

- The middle cranial fossa should be adequately decompressed to minimize the risk of uncal herniation, which may occur despite normal ICP.

- A generous durotomy must be performed, since most of the reduction in ICP is achieved by opening the dura. The dural defect is then covered using loosely applied hemostatic material or a duraplasty.

Clinical trials of decompressive craniectomy in TBI suggest that the procedure is effective in controlling ICP and is lifesaving in patients who have failed medical therapy. However, patients who require decompressive craniectomy for the management of intracranial hypertension following TBI have suffered particularly severe brain injury and may be left in a state of severe disability or worse. Conclusions from clinical trials are somewhat limited because of short follow-up time; functional recovery following severe TBI may be delayed beyond one year of follow-up. (See 'Outcomes' below.)

- A randomized trial (DECRA) in 155 adults with severe diffuse TBI and ICP >20 mmHg for 15 minutes within a one-hour period despite first-tier therapies compared bifrontal craniectomy with continued medical care [198]. Surgery was associated with a decreased burden of intracranial hypertension and shorter stays in the ICU, but worse outcome on the extended Glasgow Outcome Scale (E-GOS) at six months. Patients judged to require surgical evacuation of an intracranial hematoma were excluded, limiting the applicability of these findings. Other limitations of this trial included a low ICP threshold for eligibility, use of a very extensive bilateral craniectomy not reflective of typical clinical practice, and a baseline imbalance in patients admitted with bilateral fixed pupils suggestive of devastating injury [199].

- The RESCUEicp trial used more broadly applicable eligibility criteria; 408 patients 10 to 65 years old with refractory ICP >25 mmHg for 1 to 12 hours despite medical therapy were randomized to continued medical therapy or craniectomy appropriate to the type of injury [200]. Patients requiring hematoma evacuation were included. Control of ICP was improved in the surgical arm. At six months, patients in the surgical group had lower mortality (27 versus 49 percent) but higher rates of vegetative state (8.5 versus 2.1 percent), lower severe disability (dependent on others for care in the home; 22 versus 14 percent), and upper severe disability (independent within but not outside of the home; 15 versus 8 percent), these outcomes likely reflecting those of patients who would have not otherwise survived. Rates of moderate disability and good recovery were similar between the two groups (23 versus 20 percent and 4 versus 7 percent, respectively). The intention-to-treat analysis with 37 percent crossover from medical to surgical treatment likely diluted the apparent treatment effect. A prespecified analysis of outcomes at one year revealed that the surgical group had a higher rate of favorable outcomes (defined as better than lower severe disability or, ie, functionally independent within the home or better) of 45 versus 32 percent.

Barbiturate coma — Pentobarbital and thiopental infusions may be used to manage elevated ICP refractory to other therapies. While effective for the control of ICP, the use of barbiturate

coma has not been shown to improve outcomes following TBI [201]. Our practice is to consider barbiturate coma for ICP control only when first-line measures, including hyperosmolar therapy as well as a propofol infusion titrated to deep sedation (RASS score of -5), have been ineffective and surgical decompression is not feasible.

These agents profoundly decrease cerebral metabolic demand, CBF, and cerebral blood volume [202]. A loading dose of 5 to 20 mg/kg of pentobarbital is typically administered, followed by 1 to 4 mg/kg per hour. Continuous EEG monitoring is used, with the pentobarbital infusion titrated to produce a burst-suppression pattern. While effective for the control of ICP, pentobarbital infusions are associated with morbidity. The neurologic examination is precluded for an extended period of time because of the long half-life of this drug. This may also result in delays in the determination of brain death. Other common side effects include hypotension requiring vasopressor support, adynamic ileus, and poor pulmonary mucus clearance, with the consequent risk of ventilator-associated pneumonia [203]. Severe metabolic acidosis from propylene-glycol toxicity has been reported with the use of pentobarbital infusions [204,205].

Hypothermia — Induced or therapeutic hypothermia has been proposed as a treatment for TBI based upon its potential to reduce ICP as well as to provide neuroprotection and prevent secondary brain injury [206]. Therapeutic hypothermia does appear effective for the control of ICP [207] but has not been convincingly shown to improve outcomes. Therapeutic hypothermia treatment should, therefore, be limited to clinical trials, or to patients with elevated ICP refractory to other therapies, after discussion with family and other patient surrogates [208-210].

A systematic review of 37 randomized controlled trials, including 3110 subjects, of mild to moderate hypothermia (32 to 35°C) following TBI concluded that there was no high-quality evidence that hypothermia is beneficial following TBI for the goal of improving meaningful long-term outcomes [211]. Other systematic reviews and meta-analyses found borderline benefits for death and neurologic outcome, but also an increased risk for pneumonia [206,212-215]. Substantial variability among studies in the depth and duration of hypothermia, as well as the rate of rewarming, limits the ability to draw conclusions from these studies. Two subsequently published trials found no benefit of induced hypothermia in specific subgroups of patients with TBI; in one, hypothermia was not beneficial when initiated within two to five hours of TBI in a selected group of younger patients (age 16 to 45 years) [216]. In another trial, there was no benefit for induced hypothermia when added to other standard-of-care measures in patients with intracranial hypertension refractory to initial treatment within 10 days of TBI; deaths and unfavorable outcomes were somewhat more common in patients receiving therapeutic hypothermia [217].

Two trials of hypothermia therapy in children with TBI have shown no improvement in neurologic or other outcomes; one showed a nonsignificant increase in mortality [218,219]. (See "Elevated intracranial pressure (ICP) in children: Management", section on 'Temperature control'.)

ADVANCED NEUROMONITORING

In order to supplement intracranial pressure (ICP) monitoring, several technologies have been developed for the treatment of severe TBI. These techniques allow for the measurement of cerebral physiologic and metabolic parameters related to oxygen delivery, cerebral blood flow (CBF), and metabolism, with the goal of improving the detection and management of secondary brain injury.

While observational data suggest that these monitoring tools provide unique information that may help to individualize the management of patients with severe head injury, clinical trial data demonstrating improved outcomes with use of these multimodality advanced neuromonitoring approaches are awaited.

Such techniques include:

- Jugular venous oximetry – Retrograde cannulation of the internal jugular vein that allows measurement of oxygen saturation in the blood exiting the brain [220]. Normal jugular venous oxygen saturation ($SjVO_2$) is approximately 60 percent. $SjVO_2$ <50 percent for 10 minutes is considered a "cerebral desaturation" and implies a mismatch between oxygen delivery and demand in the brain. These desaturation episodes are associated with unfavorable neurologic outcomes in this setting [15,221,222]. Jugular venous oximetry protocols that specify stepwise escalation of therapy to improve cerebral perfusion when desaturations occur have been used at several institutions; however, randomized clinical trials have not been performed.

- Brain tissue oxygen tension ($PbtO_2$) monitoring – Intraparenchymal oxygen electrode placed in a manner similar to a fiberoptic ICP probe that measures $PbtO_2$ in the white matter [223]. Normal $PbtO_2$ is >20 mmHg; duration and depth of $PbtO_2$ below 15 mmHg are associated with worsened outcome [224]. Some studies have shown improved outcomes in patients managed with treatment protocols directed at optimization of $PbtO_2$ as compared with historical controls [225,226]. A phase 2 randomized clinical trial (BOOST-2) demonstrated the feasibility of a goal-directed management protocol for the optimization of $PbtO_2$ following TBI [227]; a phase 3 trial (BOOST-3) is underway.

- Cerebral microdialysis – Intraparenchymal probe placed in a manner similar to a $PbtO_2$ probe that allows measurement of extracellular glucose, lactate, pyruvate, and glutamate [228,229]. A lactate:pyruvate ratio >40 is suggestive of anaerobic metabolism, which is believed to exacerbate secondary brain injury.

- Thermal diffusion flowmetry – Intraparenchymal probe placed in a manner similar to a $PbtO_2$ probe that allows continuous measurement of CBF, usually in the white matter. Correlation with CBF from neuroimaging and outcome data is very preliminary at present.

- Pressure reactivity index (PRx) – The continuously monitored moving correlation coefficient between mean ICP and mean arterial pressure (MAP), used as a measure of cerebral autoregulation. A direct correlation of ICP with MAP, with a PRx close to +1.0, suggests the absence of cerebral autoregulation and may be seen with refractory intracranial hypertension. PRx thresholds of 0.25 and 0.05, suggesting the presence of robust cerebral autoregulation, predicted survival and favorable outcome, respectively, in one study [149]. The PRx has also been used to identify optimal cerebral perfusion pressure (CPP) [230] and ICP [231] goals in individual TBI patients based on quantification of cerebral autoregulation.

INTERVENTIONS WITH UNCERTAIN OR NO BENEFIT

Neuroprotective treatment — A wide range of agents targeting various aspects of the brain injury cascade has been tested in clinical trials. To date, no neuroprotective agents or strategies (including induced hypothermia) have been shown to produce improved outcome [232]. No benefit was found for intravenous (IV) progesterone administration in two randomized trials in acute severe TBI [233,234]. Citicoline was not found to be effective at improving outcomes in a randomized trial of 1213 patients with TBI [235].

Erythropoietin has been postulated to have neuroprotective effects. However, two randomized clinical trials have not demonstrated a benefit in patients with TBI [236,237]. In the larger study of 606 patients with TBI, neurologic outcome at six months was not improved, while mortality was nonsignificantly lower (11 versus 16 percent) in patients who received erythropoietin [237]. A hemoglobin transfusion of 10 g/dL did not result in improved functional outcomes at six months as compared with the usual threshold of 7 g/dL in one trial [236].

Other agents being investigated include magnesium [238], hyperbaric oxygen [239], and cyclosporine [240], among others [241].

Glucocorticoids — The use of glucocorticoid therapy following head trauma was found to be harmful in a large trial of patients with moderate to severe TBI [242]. More than 10,000 patients were randomly assigned to treatment with methylprednisolone or to placebo within eight hours of presentation. Patients treated with glucocorticoids had increased mortality at two weeks (21 versus 18 percent; relative risk [RR] 1.18) and at six months (26 versus 22 percent; relative risk [RR] 1.15) [243].

PROGNOSIS

Outcomes

- **Severe TBI** – Cohort studies have suggested that patients with severe head injury (Glasgow Coma Scale [GCS] score ≤8) have approximately a 30 percent risk of death. At least one cohort study found that survivors of TBI continue to have a substantially increased risk of mortality for at least 13 years after the trauma [244].

  Multiple studies indicate, however, that significant proportions (30 to 65 percent) of patients with severe TBI will regain an independence, and that functional recovery following severe TBI can occur very slowly, extending beyond even 6 to 12 months [245-253]. In one Australian study, one-quarter of patients who were severely disabled or vegetative at six months following decompressive craniectomy for TBI improved to a state of moderate disability or better by 18 months [254].

  Approximately 5 to 15 percent of patients with severe TBI are discharged from acute care in a vegetative state [255-257]. Only half of these patients regain consciousness over the next year, and virtually all of these patients remain severely disabled. Outcomes are somewhat better for those in minimally conscious state. The persistent vegetative and minimally conscious states are described separately. The use of prognostic indicators for these outcomes is better defined for hypoxic-ischemic brain injury than for TBI [258].

  A randomized trial of amantadine (starting at 100 mg twice daily) in 184 patients admitted to inpatient rehabilitation in a vegetative or minimally conscious state after severe TBI found that amantadine treatment was associated with accelerated recovery during the four-week active treatment phase [259]. Rates of improvement subsequently slowed after treatment withdrawal in the amantadine group, and at week 6, disability scores in the two groups were similar. Further study is needed to determine a benefit for amantadine on long-term prognosis and its role in the treatment of patients with severe TBI. The mechanism of action for putative beneficial effect of amantadine is unclear; it is

speculated that antagonism of N-methyl-D-aspartate and/or indirect agonism of dopamine may be involved.

- **Moderate TBI** – The prognosis of patients with moderate TBI is less well studied but is not uniformly benign: mortality is approximately 15 percent, cognitive sequelae may occur in over half, and only approximately 20 percent return to their baseline level of functioning [7,8,260-263]. Among patients with moderate TBI, pretrauma, educational attainment is associated with increased odds of disability-free recovery [264].

Individual risk factors — Outcome from severe head injury is dependent on a range of factors including baseline patient characteristics, severity of TBI, and the occurrence of medical complications and secondary brain insults. While many individual negative outcome predictors have been identified, each is associated with a significantly high false-positive rate and must not be used in isolation to estimate a prognosis.

Identified risk factors include [25,28,29,31,120,140,232,256,265-273]:

- GCS score at presentation (especially the GCS motor score) (table 1)
- Full Outline of UnResponsiveness (FOUR) score (table 2)
- Presence of severe CT abnormalities (high-grade subarachnoid hemorrhage, cisternal effacement, midline shift, leukoaraiosis)
- Pupillary function
- Age
- Associated extracranial injuries and complications
- Hypotension
- Hypoxemia
- Pyrexia
- Elevated intracranial pressure (ICP)
- Reduced cerebral perfusion pressure (CPP)
- Bleeding diathesis (low platelet count, abnormal coagulation parameters)

Magnetic resonance imaging (MRI) has also been studied as a prognostic tool following TBI [274-277]; diffuse axonal injury (DAI) and brainstem injury on MRI may predict poor long-term functional outcomes [278,279]. However, favorable outcomes may occur despite the presence of lesions on MRI traditionally thought to portend a poor prognosis [280], and MRI should not be used in isolation to guide prognostication following severe TBI.

Other studies are evaluating the potential of biomarkers, such as the levels of S-100β protein, neuron-specific enolase, and α-synuclein in the blood and/or cerebrospinal fluid (CSF), to predict neurologic outcome [281-283].

Outcome prediction models — Outcome prediction models derived from large datasets, incorporating multiple predictors, have been developed and have undergone external validation [269,284-286]. However, it is important to recognize that all outcome prediction models in neurologic injury are prone to confounding by self-fulfilling prophecies (where the presence of variables widely considered to be predictors of poor outcome lead to the delivery of an unfavorable prognosis to the family with consequent withdrawal of life support) within the datasets of patients used to develop and validate the model. A group of investigators in Sweden has described an overestimation of both mortality and poor outcomes in patients managed aggressively with an ICP-targeted treatment protocol [287,288].

Therefore, except in the most extreme cases, a trial of early aggressive neurosurgical and neurocritical care management, including surgical removal of evacuable lesions and ICP monitoring, should be undertaken in patients with severe TBI.

The two most widely used publicly available prediction models are the International Mission for Prognosis and Analysis of Clinical Trials in TBI (IMPACT) and Corticosteroid Randomisation After Significant Head Injury (CRASH) models:

- The CRASH prediction model was derived from the large international clinical trial of glucocorticoids in TBI with 10,008 subjects from high-, middle-, and low-income countries [289]. Variables in this model include country, age, GCS, pupillary reactivity, the presence of significant extracranial injury, and specific findings on CT.

- The IMPACT model was developed using data from 8509 patients in 11 studies [290]. The variables in this model include age, GCS motor score, and pupillary reactivity as core clinical variables, as well as the occurrence of hypoxia and hypotension, the Marshall CT grade (table 5) plus other CT findings, and glucose and hemoglobin levels.

These models have been validated in large cohorts of patients, and may have more limited applicability to individual prognostication.

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Increased intracranial pressure and moderate-to-severe traumatic brain injury".)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topic (see "Patient education: Head injury in adults (The Basics)")

SUMMARY AND RECOMMENDATIONS

- **Definitions and triage** – Patients with moderate (Glasgow Coma Scale [GCS] score 9 through 13) and severe (GCS score <9) traumatic brain injury (TBI) are most optimally managed in a specialized neurotrauma center with neurosurgical and neurocritical care support and the use of guidelines-based protocols.

- **Prehospital care** – Prevention of hypoxia (PaO_2 <60 mmHg) and hypotension (systolic blood pressure [BP] <100 mmHg) are priorities in the management of patients with moderate or severe TBI beginning during their prehospital care. (See 'Initial evaluation and treatment' above.)

- **Emergency department care** – Patients with TBI and GCS score <9 should undergo endotracheal intubation in the emergency department (ED), if not before. Specific considerations exist when performing endotracheal intubation in patients with suspected elevation in intracranial pressure (ICP). Multiple factors must be considered when making decisions about prehospital intubation of patients with moderate or severe TBI. (See 'Prehospital' above and 'Emergency department' above.)

  ED evaluation should include frequent clinical neurologic assessments and a CT scan of the head. (See 'Emergency department' above.)

- **Antifibrinolytic therapy** – For patients with moderate TBI presenting to the ED within three hours of injury, we recommend immediate administration of tranexamic acid (**Grade**

1B). Tranexamic acid (1 g infused over 10 minutes, followed by an intravenous infusion of 1 g over eight hours) is associated with reduced mortality in patients with moderate TBI. Prehospital administration of tranexamic acid is not recommended.

The use of tranexamic acid in patients can be considered in other patient groups; however, the impact on mortality is uncertain in these patients. (See 'Antifibrinolytic therapy' above.)

- **Ventilation** – Hyperventilation should be avoided in the first 24 to 48 hours and should not exceed $PaCO_2$ <30 mmHg except as a temporizing measure in a patient with impending cerebral herniation. Positive end-expiratory pressure (PEEP) up to 15 to 20 cm H_2O may be utilized to manage acute respiratory distress syndrome (ARDS) following TBI while ICP is monitored. (See 'Ventilation' above.)

- **Surgery** – Surgical evacuation of epidural, subdural, and intracerebral hematomas should be decided based upon hematoma volume and associated mass effect, in conjunction with the patient's neurologic status. (See 'Surgical treatment' above.)

- **Intracranial pressure management**

  - **Impending herniation** – Impending cerebral herniation is an emergency and manifests with unilateral or bilateral fixed and dilated pupils, decorticate or decerebrate posturing, respiratory depression, and the "Cushing triad" of hypertension, bradycardia, and irregular respiration.

    When impending herniation due to elevated ICP is suspected, we recommend empiric interventions including endotracheal intubation, head of bed (HOB) elevation, and hyperventilation.

    We also recommend bolus dose of 23.4 percent sodium chloride or mannitol pending the results of the CT and measurement of ICP (**Grade 1C**). (See 'Patients with impending cerebral herniation' above.)

  - **ICP monitoring and management** – For patients with severe TBI and an abnormal CT scan showing evidence of mass effect from lesions such as hematomas, contusions, or swelling, we suggest ventriculostomy and ICP monitoring along with treatment of elevated ICP to target pressures below 22 mmHg (**Grade 2C**). (See 'ICP and CPP monitoring' above.)

    Appropriate first measures include removal of cerebrospinal fluid (CSF) through the ventriculostomy, HOB elevation, and analgesia and sedation, followed by osmotic therapy with either hypertonic saline or mannitol. (See 'Initial (baseline) treatment'

above and 'Cerebrospinal fluid drainage' above and 'Sedation and analgesia' above and 'Osmotic therapy' above.)

- **Refractory ICP elevation** – For patients with elevated ICP refractory to initial therapy, options include decompressive craniectomy, barbiturate coma, and induced hypothermia. Such patients have a poor prognosis; further interventions should be based on a risk-benefit discussion with family. (See 'Refractory ICP elevation' above.)

- **Fluid and hemodynamic management** – We suggest using normal saline rather than colloid solutions to maintain euvolemia (**Grade 2B**).

  Other management strategies prioritize avoiding hypotension and maintaining cerebral perfusion pressure (CPP). (See 'Hemodynamic management' above.)

- **Seizure prevention and treatment** – We recommend one-week use of antiseizure medications to prevent early seizures (**Grade 1B**). Patients with seizures should be treated to prevent recurrence.

  We suggest levetiracetam for prevention and treatment of seizures (**Grade 2C**); other antiseizure medications (eg, fosphenytoin) that can be provided parenterally are reasonable alternatives. (See 'Antiseizure medications and electroencephalography monitoring' above and "Posttraumatic seizures and epilepsy".)

- **Other aspects of supportive care** – Fever and hyperglycemia should be avoided for their potential to exacerbate secondary neurologic injury. Nutritional support to caloric goals should be achieved by day 5 from injury using enteral nutrition. Coagulopathy should be corrected to maintain an international normalized ratio (INR) <1.4 and a platelet count >75,000/mm^3. (See 'Temperature management' above and 'Glucose management' above and 'Nutritional support' above and 'Management of coagulopathy' above.)

- **Paroxysmal sympathetic hyperactivity (PSH)** – PSH, characterized by episodes of hypertension, tachycardia, and other dysautonomias, may occur following TBI and correlates with severity of injury. (See "Paroxysmal sympathetic hyperactivity".)

- **Venous thromboembolism (VTE) prophylaxis** – We recommend mechanical thromboprophylaxis with intermittent pneumatic compression for the prevention of VTE (**Grade 1A**). The use and timing of antithrombotic agents is individualized based upon an assessment of the competing risks of venous thrombosis and intracranial hemorrhage expansion. (See 'Hemodynamic management' above.)

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Topic 4826 Version 34.0

GRAPHICS

Glasgow Coma Scale (GCS)

	Score
Eye opening	
Spontaneous	4
Response to verbal command	3
Response to pain	2
No eye opening	1
Best verbal response	
Oriented	5
Confused	4
Inappropriate words	3
Incomprehensible sounds	2
No verbal response	1
Best motor response	
Obeys commands	6
Localizing response to pain	5
Withdrawal response to pain	4
Flexion to pain	3
Extension to pain	2
No motor response	1
Total	

The GCS is scored between 3 and 15, 3 being the worst and 15 the best. It is composed of three parameters: best eye response (E), best verbal response (V), and best motor response (M). The components of the GCS should be recorded individually; for example, E2V3M4 results in a GCS score of 9. A score of 13 or higher correlates with mild brain injury, a score of 9 to 12 correlates with moderate injury, and a score of 8 or less represents severe brain injury.

Graphic 81854 Version 9.0

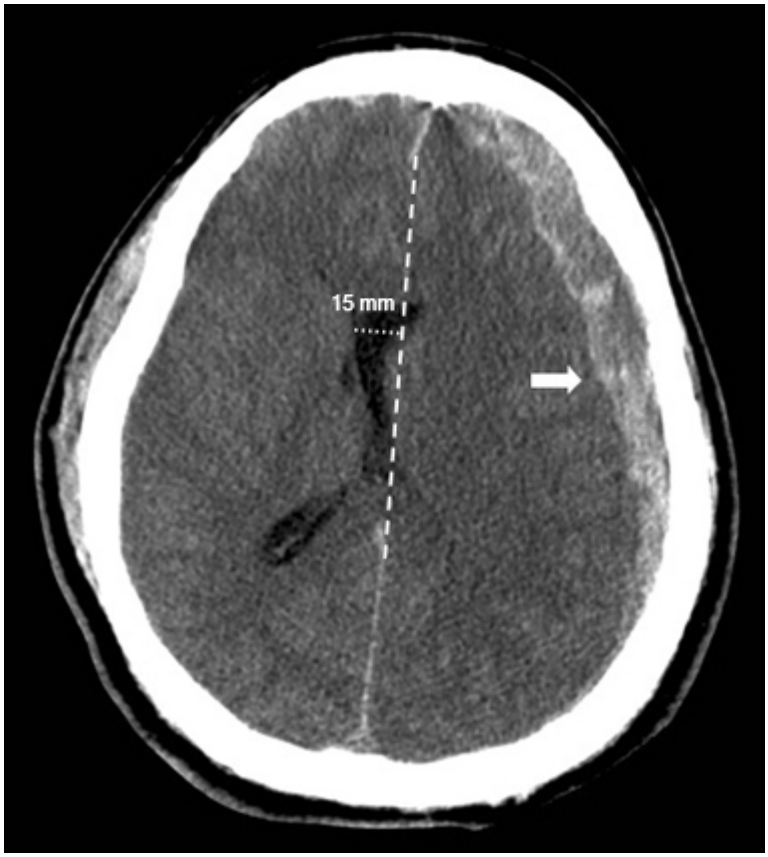
FOUR score

Eye response
4 = eyelids open or opened, tracking, or blinking to command
3 = eyelids open but not tracking
2 = eyelids closed but open to loud voice
1 = eyelids closed but open to pain
0 = eyelids remain closed with pain
Motor response
4 = thumbs-up, fist, or peace sign
3 = localizing to pain
2 = flexion response to pain
1 = extension response to pain
0 = no response to pain or generalized myoclonus status
Brainstem reflexes
4 = pupil and corneal reflexes present
3 = one pupil wide and fixed
2 = pupil or corneal reflexes absent
1 = pupil and corneal reflexes absent
0 = absent pupil, corneal, and cough reflex
Respiration
4 = not intubated, regular breathing pattern
3 = not intubated, Cheyne-Stokes breathing pattern
2 = not intubated, irregular breathing
1 = breathes above ventilator rate
0 = breathes at ventilator rate or apnea

FOUR score: Full Outline of UnResponsiveness.

Graphic 62673 Version 4.0

Traumatic subdural hematoma (SDH)

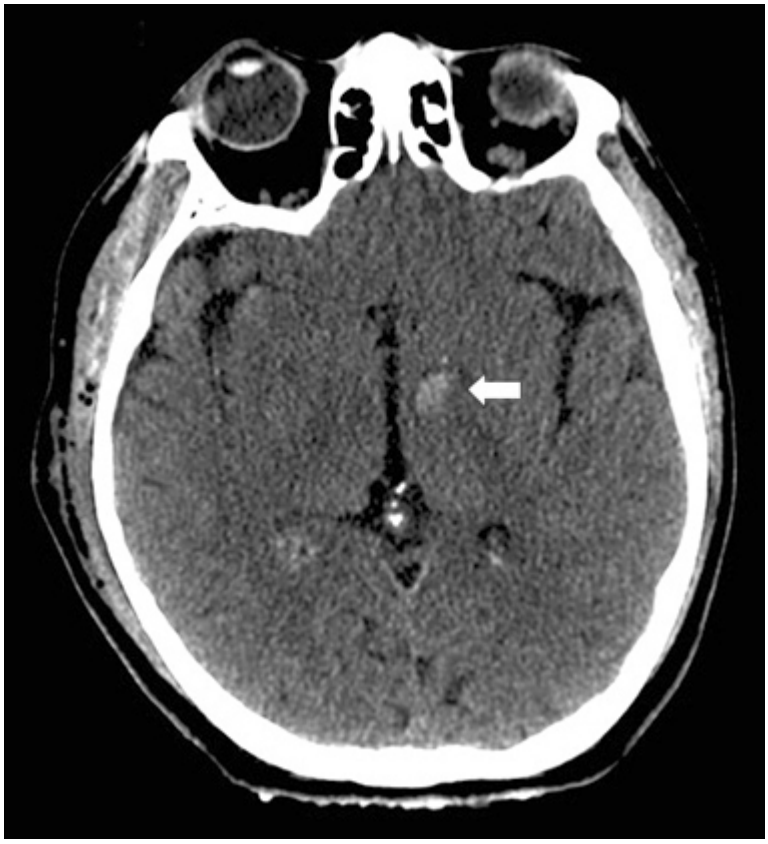


CT scan showing a left acute SDH (arrow). SDHs are typically crescent shaped. In this case the SDH is causing significant mass effect and shift of midline structures to the right.

CT: computed tomography.

Graphic 68102 Version 5.0

Diffuse axonal injury (DAI)

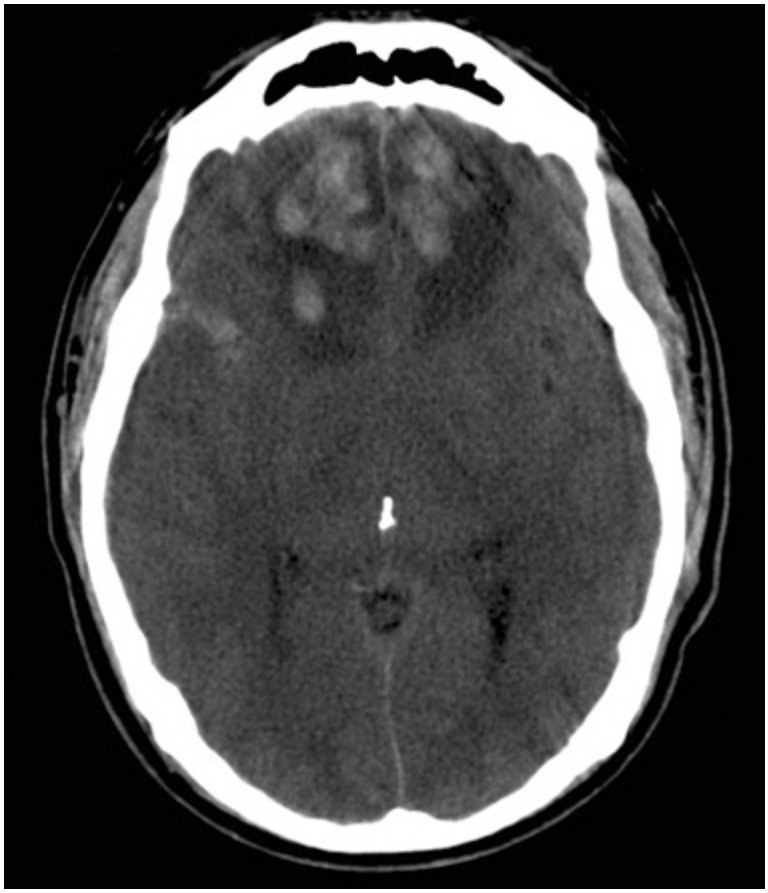


CT scan of the brain showing DAI. Note the deep shearing-type injury in or near the white matter of the left internal capsule (arrow).

CT: computed tomography.

Graphic 67573 Version 5.0

Frontal cerebral contusion

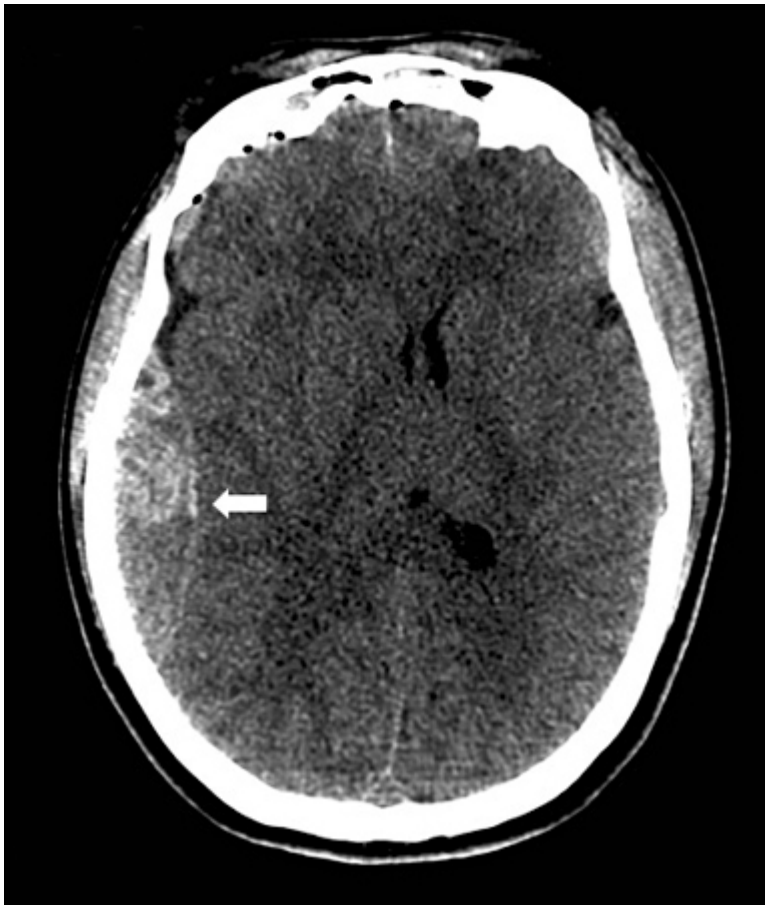


CT scan of the brain depicting cerebral contusions. The basal frontal areas (as shown) are particularly susceptible.

CT: computed tomography.

Graphic 53951 Version 4.0

Traumatic epidural hematoma (EDH)

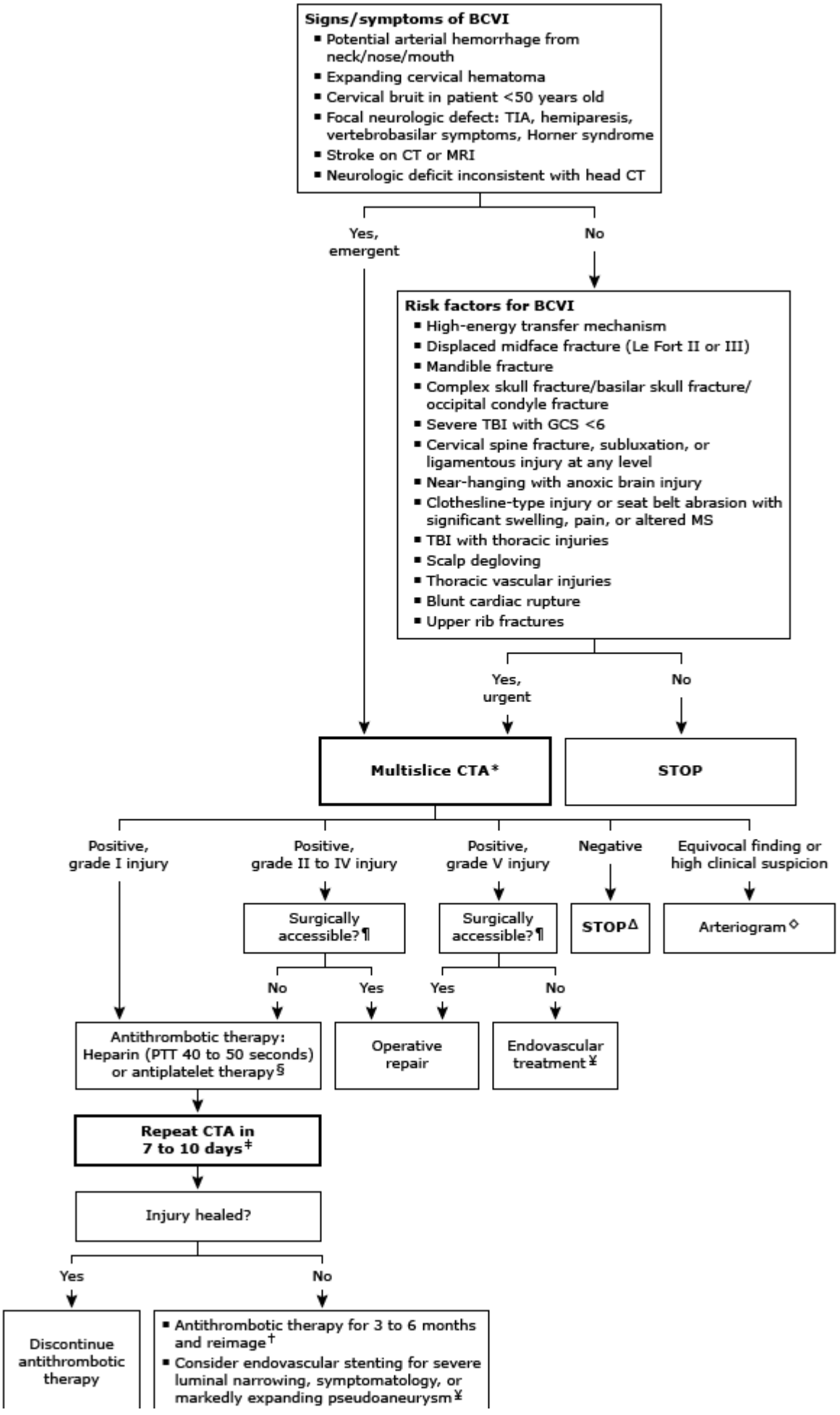


CT scan demonstrating a right EDH (arrow). Note the lenticular shape.

CT: computed tomography.

Graphic 56200 Version 5.0

Algorithm for diagnosis and management of blunt cerebrovascular injury


Signs/symptoms of BCVI
Potential arterial hemorrhage from neck/nose/mouth
Expanding cervical hematoma
Cervical bruit in patient <50 years old
Focal neurologic defect: TIA, hemiparesis, vertebrobasilar symptoms, Horner syndrome
Stroke on CT or MRI
Neurologic deficit inconsistent with head CT
Yes, emergent
No
Risk factors for BCVI
High-energy transfer mechanism
Displaced midface fracture (Le Fort II or III)
Mandible fracture
Complex skull fracture/basilar skull fracture/ occipital condyle fracture
Severe TBI with GCS <6
Cervical spine fracture, subluxation, or ligamentous injury at any level
Near-hanging with anoxic brain injury
Clothesline-type injury or seat belt abrasion with significant swelling, pain, or altered MS
TBI with thoracic injuries
Scalp degloving
Thoracic vascular injuries
Blunt cardiac rupture
Upper rib fractures
Yes, urgent
No
Multislice CTA*
STOP
Positive, grade I injury
Positive, grade II to IV injury
Positive, grade V injury
Negative
Equivocal finding or high clinical suspicion
Surgically accessible?¶
Surgically accessible?¶
STOPΔ
Arteriogram◇
No
Yes
Yes
No
Antithrombotic therapy: Heparin (PTT 40 to 50 seconds) or antiplatelet therapy§
Operative repair
Endovascular treatment¥
Repeat CTA in 7 to 10 days‡
Injury healed?
Yes
No
Discontinue antithrombotic therapy
Antithrombotic therapy for 3 to 6 months and reimage†
Consider endovascular stenting for severe luminal narrowing, symptomatology, or markedly expanding pseudoaneurysm¥

BCVI: blunt cerebrovascular injury; TIA: transient ischemic attack; CT: computed tomography; MRI: magnetic resonance imaging; TBI: traumatic brain injury; GCS: Glasgow coma scale; MS: mental status; CTA: computed tomographic angiography; PTT: partial thromboplastin time; DSA: digital subtraction angiography.

* CTA with multidetector-row CT; 64-channel is optimal. If fewer than 16 channels, interpret CT angiogram with caution; DSA is the gold standard.

¶ Patient has not suffered completed stroke.

Δ If signs/symptoms or high clinical suspicion and negative CTA, consider DSA.

◊ For positive arteriogram (DSA), follow treatment algorithm per multislice CTA results.

§ Heparin is preferred in the acute setting as it is reversible and may be more effective than antiplatelet agents. Anticoagulation may be contraindicated due to other injuries. Antiplatelet therapy is typically aspirin 325 mg daily.

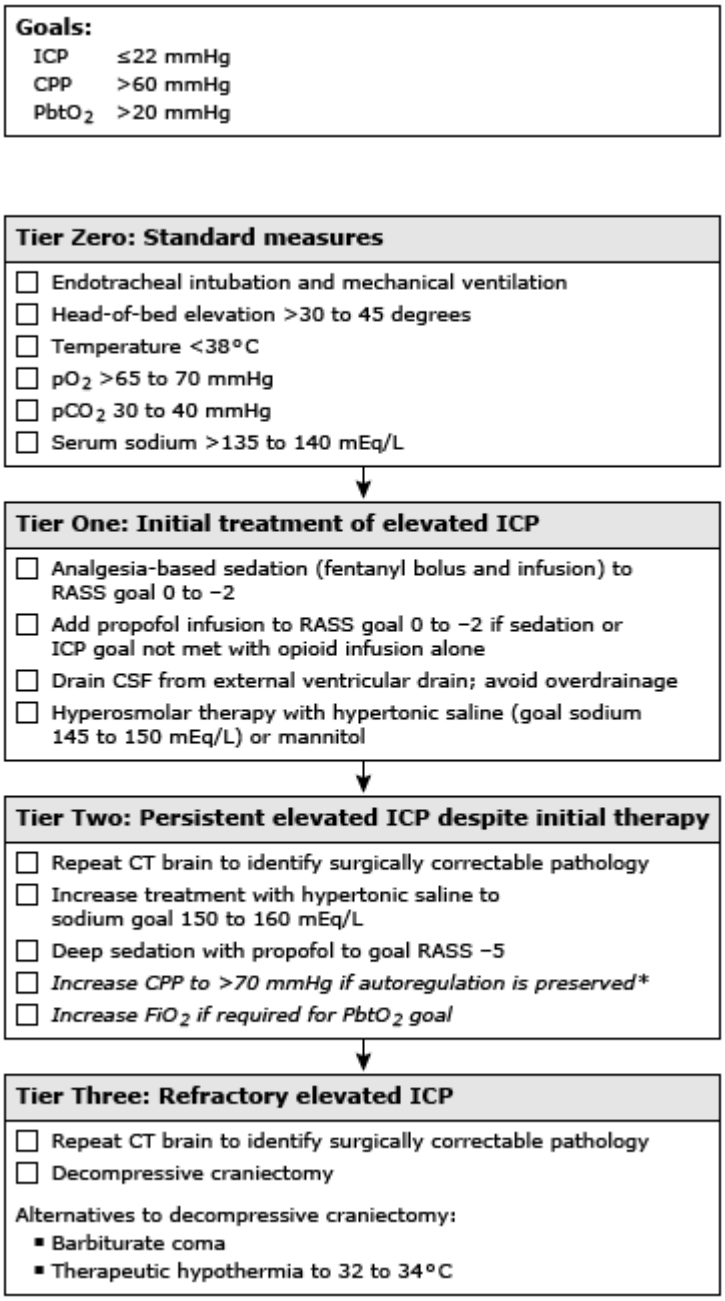
¥ Stenting should be performed with caution and appropriate antithrombotic therapy administered concurrently.

‡ If symptomatic common carotid fistula, consider arteriography and endovascular therapy. If asymptomatic common carotid fistula, reimage with CTA at three to four weeks.

† Aspirin alone (325 mg daily) is adequate and should be considered lifelong as its risk profile is superior to warfarin.

Graphic 78174 Version 13.0

Stepwise management of elevated ICP in patients with severe TBI (Glasgow Coma Scale <9)



ICP: intracranial pressure; TBI: traumatic brain injury; CPP: cerebral perfusion pressure; $PbtO_2$: brain tissue oxygen; pO_2: partial pressure of oxygen; pCO_2: partial pressure of carbon dioxide; RASS: Richmond Agitation-Sedation Scale; CSF: cerebrospinal fluid; CT: computed tomography; FiO_2: fraction of inspired oxygen.

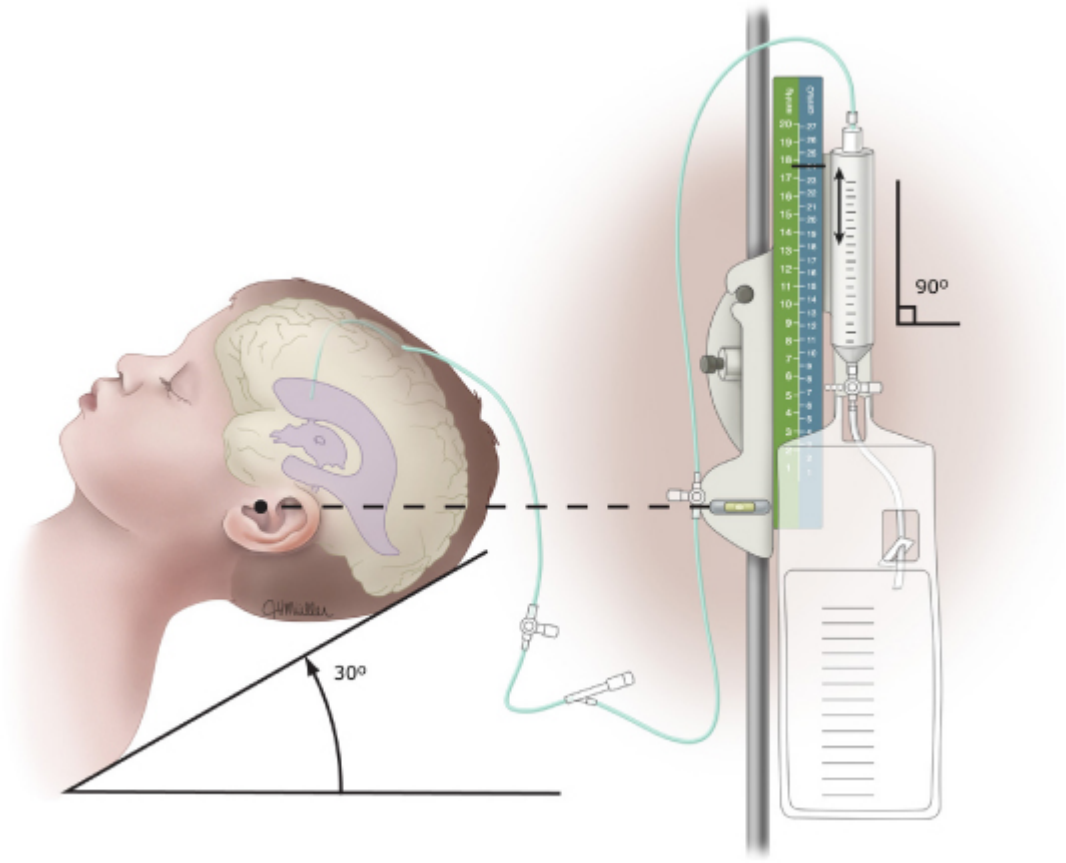
* If advanced monitoring available.

Adapted from: Cadena R, Shoykhet M, Ratcliff JJ. Emergency Neurological Life

Support: Intracranial Hypertension and Herniation. Neurocrit Care 2017; 27:82.

Graphic 121359 Version 1.0

External ventricular drain



An external ventricular drain (EVD) is a small catheter inserted through the skull usually into the lateral ventricle, which is typically connected to a closed collecting device to allow for drainage of cerebrospinal fluid. The EVD can also be connected to a transducer that records intracranial pressure.

Graphic 56391 Version 2.0

Richmond Agitation-Sedation Scale (RASS)

Score	Term	Description
+4	Combative	Overtly combative or violent, immediate danger to staff
+3	Very agitated	Pulls on or removes tubes or catheters, aggressive behavior toward staff
+2	Agitated	Frequent nonpurposeful movement or patient-ventilator dyssynchrony
+1	Restless	Anxious or apprehensive but movements not aggressive or vigorous
0	Alert and calm	
-1	Drowsy	Not fully alert, sustained (>10 seconds) awakening, eye contact to voice
-2	Light sedation	Briefly (<10 seconds) awakens with eye contact to voice
-3	Moderate sedation	Any movement (but no eye contact) to voice
-4	Deep sedation	No response to voice, any movement to physical stimulation
-5	Unarousable	No response to voice or physical stimulation
Procedure		
1.	Observe patient. Is patient alert and calm (score 0)?	
2.	Does patient have behavior that is consistent with restlessness or agitation?	
	Assign score +1 to +4 using the criteria listed above.	
3.	If patient is not alert, in a loud speaking voice state patient's name and direct patient to open eyes and look at speaker. Repeat once if necessary. Can prompt patient to continue looking at speaker.	
	Patient has eye opening and eye contact, which is sustained for more than 10 seconds (score -1).	
	Patient has eye opening and eye contact, but this is not sustained for 10 seconds (score -2).	
	Patient has any movement in response to voice, excluding eye contact (score -3).	
4.	If patient does not respond to voice, physically stimulate patient by shaking shoulder and then rubbing sternum if there is no response.	
	Patient has any movement to physical stimulation (score -4).	
	Patient has no response to voice or physical stimulation (score -5).	

Thoracic Society.

Graphic 57874 Version 2.0

Intravenous* sedative and analgesic dosing regimens for managing pain, agitation, and delirium in the intensive care unit

Drug	Loading dose	Maintenance dose range	Onset (minutes)	Duration of intermittent dose (minutes)	Charact and
Opioid analgesics					
Fentanyl	1 to 2 mcg/kg¶ (25 to 100 mcg)	0.35 to 0.5 mcg/kg every 0.5 to 1 hour intermittent (25 to 50 mcg) **and/or** 0.7 to 10 mcg/kg/hour infusion[1] For most patients, 1 to 3 mcg/kg/hour infusion (50 to 300 mcg/hour) with as-needed intermittent bolus doses is sufficient	<1 to 2	30 to 60Δ	**Advanta** Potent ar sedative immedia and less hypotens other opi analgesic due to re lack of hi release. Metaboli hepatical CYP3A4 t metaboli **Disadvar** Highly lip parent dr accumula adipose a tissue wit repeated prolonge administ Chest wa may occu higher do **Role:** A g choice fo analgesia most crit patients.
Hydromorphone	0.5 to 2 mg¶	0.2 to 0.6 mg every 1 to 2	5 to 10	240 to 300	**Advanta** administ

		hours intermittent **and/or** 0.5 to 3 mg/hour infusion			requires volumes to other Non-CYP metaboli (glucuror may be a advantag patients drugs tha significar CYP3A4 metaboli thereby i with fent **Disadvar** Potential neurotox (excitator metaboli accumula hepatic a renal dysfunct **Role:** Ana option al to fentan morphine adjustme gradual t needed f patients renal and hepatic impairme
Morphine sulfate	2 to 10 mg¶	2 to 4 mg every 1 to 2 hours intermittent **and/or** 2 to 30 mg/hour infusion	5 to 10	240 to 300	**Advanta** CYP meta (glucuror may be a advantag selected receiving that sign alter CYP metaboli

						thereby i with fent **Disadvar** Can accu hepatic o dysfuncti prolong e Histamin and vaga mediatec venodilat hypotens bradycar be signifi **Role:** Ana alternativ fentanyl hydromo where pr reductior myocardi depressiv are desir tolerable adjustme gradual t needed f patients renal and hepatic impairme in patient advanced decompe liver dise renal imp due to ris accumula neurotox metaboli Infusions generally sedation analgesia ICU but a

					common for pallia purpose
Remifentanil	Optional: 1.5 mcg/kg[1] Most ICU patients can be managed without bolus doses; if required, a bolus of 0.5 mcg/kg is usually sufficient; larger boluses are associated with significant reductions in HR and MAP	0.5 to 15 mcg/kg/hour infusion	1 to 3	5 to 10 (after cessation of infusion)	**Advanta** Ultra-sho Cleared b nonspeci plasma e to inactiv metaboli not accu renal or h impairme Prompt r analgesia sedation discontin **Disadvar** Anticipat and disc upon abr cessation excipient accumula renal impairme **Role:** An alternati fentanyl f patients r frequent neurolog assessme those wit multiorga failure.
Nonopioid analgesics (adjunctive or opioid sparing)					
Acetaminophen (paracetamol)	None	Oral, rectal: 325 to 1000 mg every 4 to 6 hours IV: 650 mg IV every 4 hours to 1000 mg IV	Oral: 30 to 60 Rectal: Variable IV: 5 to 10	240 to 360	**Advanta** Lacks dep and toler opioids. L antiplate and

		every 6 hours, or 15 mg/kg IV every 6 hours for patients weighing <50 kg Maximum ≤4 g/day			gastroint toxicity o **Disadvar** Lacks sig anti-infla effect. IV preparati requires administ over 15 n Can caus hepatoto chronic o overdose or use a l daily dos adults an patients hepatoto heavy alc or malno Interacts warfarin prolong I CYP-indu drugs (el risk of he inflamma **Role:** Firs for treatr mild to m acute pai febrile co Adjunctiv analgesic may redu requirem When he dysfuncti significar consider or reduci (eg, ≤2 g/ total).

Ketorolac	Optional: 30 mg once	Age <65 years and weight ≥50 kg: 15 to 30 mg every 6 hours; maximum 120 mg/day for up to 5 days Age ≥65 years or weight <50 kg: 15 mg every 6 hours; maximum 60 mg/day for up to 5 days	IV: ~30	360 to 480	**Advanta** Lacks dep and toler opioids. E anti-infla **Disadvar** Can caus worsen r insufficie Dose-rela of gastro Reversibl platelet functioni alter cardiopro effect of **Role:** Adj analgesic may redu requirem Avoid in r impairme gastroint bleeding, dysfuncti ischemic disease, l failure, re cardiac o hypovole state, ast cirrhosis. Contrainc treatmen periopera in corona bypass gr surgery. I should be hydrated
Ibuprofen	None	Oral: 400 mg orally every 4 hours	Oral: 30 IV: ~30	240 to 360	**Advanta** Lacks dep and toler

		(maximum 2.4 g/day chronic) IV: 400 to 800 mg IV every 6 hours (maximum 3.2 g/day acute)			opioids. E anti-infla **Disadvar** Can caus worsen r insufficie Dose-rela of gastro Reversibl platelet functioni alter cardiopro effect of **Role:** Sho treatmen moderate pain and condition Adjunctiv analgesic may redu requirem Avoid in impairme gastroint bleeding, dysfuncti ischemic disease, l failure, re cardiac o hypovole state, ast cirrhosis. Contrain treatmen periopera in corona bypass g surgery. should b hydrated
Gabapentin	None	Oral: Initially 100 mg 3 times	Variable	–	**Advanta** Effective

		per day Oral: Maintenance 900 to 3600 mg per day in 3 divided doses			treatmen neuropat Low risk interactic **Disadvar** Requires administ schedule and indiv titration to weeks bioavaila variable (60%) and inversely proportic dose. Ad effects in sedation, dizziness ataxia, w be intens renal imp requiring adjustme Should n abruptly due to ris discontin symptom **Role:** Use adjunct t analgesic treatmen neuropat postoper pain or dysesthe patients be treate enteral medicati adjustme needed f impairme

Pregabalin	None	Oral: Initially 75 mg once or twice per day Oral: Maintenance 150 to 300 mg twice per day	Variable (hours to days)	–	**Advanta** Effective treatmen neuropat Oral bioa (>90%) is reliable t gabapen may prov more rap of analge a shorter of time n titrate to Low risk interactic **Disadvar** Requires administr schedule and titrat days to w Adverse include s blurred v mouth, d and ataxi may be ir in renal impairme requiring adjustme Should n abruptly due to ris discontin symptom **Role:** Use adjunct t analgesic treatmen neuropat postoper pain or dysesthe

					patients
be treate
enteral
medicati
adjustme
needed f
impairme
Anesthetic-sedative					
Propofol	Bolus doses are usually not given in the ICU	5 to 50 mcg/kg/**minute** Titrate every 5 to 10 minutes in increments of 5 to 10 mcg/kg/**minute** Some patients require up to 70 mcg/kg/minute, which can increase risk of propofol infusion syndrome (refer to UpToDate topics on sedative-analgesic medications in critically ill patients: properties, dose regimens, and adverse effects)	<1 to 2	3 to 10[Δ]	**Advanta**
Potent se
hypnotic
associate
immediat
and rapic
awakenir
discontin
when
administ
short-ter
Metaboli
reported
unaltered
hepatic o
impairme
subject t
significar
interactic
Infusion
titratable
desired d
sedation,
minimizir
oversedat
Propofol
effectivel
decrease
intracran
pressure,
cerebral
metaboli
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seizures,
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myocardi
contracti
elevated
triglyceri
peripher
injection
and rarel
propofol
syndrom
to UpToD
topics on
sedative-
medicati
critically i
patients:
propertie
regimens
adverse e
Specific p
presenta
may inclu
potential
allergens
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Role: A g
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					analgesia short-ter sedation patients i rapid awa is advant Also a go choice to elevated intracran pressure short-ter sedation general c care popu that is lik ready soc ventilato weaning
Ketamine	0.25 to 0.5 mg/kg bolus IV Bolus doses may be given prior to sedation with an infusion of ketamine or as a single bolus (eg, patients with burns prior to dress changes or for procedural sedation) Bolus dosing may be repeated if necessary during the procedure (maximum dose 2 mg/kg in a 30 minute period)	0.05 to 0.4 mg/kg/hour	≤1	10 to 15 (single dose)	**Advanta** potent dissociati sedative-anesthet marked a that mair cardiac o and MAP inhibitior respirato Does not protectiv reflexes. reduce a opioid to **Disadvar** Sympath stimulati increased myocardi oxygen d elevated intracran pressure systemic

						pressure) intolerab dependir clinical se Rarely, cardiores depressic associate rapid administr higher dc Adverse e may inclu hallucina delirium withdraw clonic moveme dissociati experien unpleasa hypersali nausea, a vomiting Complex metaboli includes 2C9, 2B6, non-CYP transforn and an ac metaboli (norketar which ma accumula renal and hepatic impairme due to dr interactic **Role:** An choice fo postsurg manager severe ag or as an

					adjunctiv analgesic patients v severe re pain in cl settings v increased myocardi oxygen d and symp tone are
Central alpha$_2$ agonist					
Dexmedetomidine	Optional: 1 mcg/kg over 10 minutes if hemodynamically stable Usually not given	0.2 to 1.5 mcg/kg/hour Initiate at 0.2 mcg/kg/hour and titrate every 30 minutes	5 to 10 (optional loading dose) 15 (without loading dose)	60 to 120	**Advanta** Effective sympath (central a agonist) v moderate anxiolysis analgesia Characte depth of may perr critically i mechanic ventilated patients t interactiv easily aw yet comf Can be us non-mec ventilated patients a continue needed f extubatic Reduces in the rev phase of hypother following resuscita cardiac a May be le

						to cause than othe sedative **Disadvar** Potential significar hypotens bradycar hyperten do not re quickly u abrupt discontin Metaboli: hepatical glucuron and CYP2 reductior recomme with rena hepatic impairme administ loading d be associ cardiovas instabilit tachycar bradycar heart blo not induc deep sed needed f neuromu blockade **Role:** A g choice fo and long sedation critically i patients relevant conditior be useful sedation

					patients v high risk developir delirium, this has r well estal
Benzodiazepines					
Midazolam	0.01 to 0.05 mg/kg[¶] (0.5 to 4 mg; this non-weight based dosing may be preferred)	0.02 to 0.1 mg/kg/hour infusion (2 to 8 mg/hour; this non-weight based dosing may be preferred) with intermittent bolus dose(s) if needed. While the patient is on a continuous infusion, periodic re-bolus may be needed to maintain the sedation goal. This approach may help prevent unnecessary dose creep of the infusion.	2 to 5	30[Δ]	**Advanta** potent ar and anxi agent wit immedia of action short dur effect wh administ short ter hours). It only IV benzodia that is no delivered propylen **Disadvar** Hepatica metaboli CYP3A4 t metaboli may accu and caus prolonge sedation delivered term. Hal be prolor critically i patients v hepatic o impairme of deliriu it interac drugs us ICU (eg, s antiretro azole ant

					that alter metaboli that exce sedation occur wit concomit of midaz drugs metaboli CYP3A4. **Role:** A g choice fo term anx and treat acute agi Dose adj and grad titration needed f patients renal and hepatic impairme
Lorazepam	0.02 to 0.04 mg/kg[¶] (1 to 2 mg; this non-weight based dosing may be preferred) If rapid effect is needed, actual body weight is sometimes used	0.02 to 0.06 mg/kg every 2 to 6 hours intermittent (1 to 4 mg) **and/or** 0.01 to 0.1 mg/kg/hour infusion (0.5 to 10 mg/hour) Non-weight based dosing may be preferred	15 to 20	360 to 480[Δ]	**Advanta** Sedative, amnestic anxiolysis anticonv propertie Hepatica metaboli glucuron inactive metaboli Relatively of drug interactic safety in moderate and rena impairme **Disadvar** Relatively onset. Ris overseda

						when titr to delaye response accumula peripher Risk of de IV incompat and risk c precipitat Propylen solvent m accumula prolonge high dosi causing r acidosis a organ dy (refer to t topics on sedative- medicati critically i patients: propertie regimens adverse e Long half significar accumula older adu patients v significar or hepati impairme **Role:** A g choice fo sedation anxiolysis most pat including who may long-tern ongoing Although intermitt

					dosing m preferrec continuo infusion r initiated patients r frequentl repeated dosing.
Diazepam	0.05 to 0.2 mg/kg[¶] (5 to 10 mg)	0.03 to 0.1 mg/kg every 0.5 to 6 hours intermittent (1 to 7 mg) Continuous infusion is not recommended	2 to 5	20 to 60[Δ]	**Advanta** Rapid on potent se and musc relaxant **Disadvar** Hepatica metaboli CYP2C19 to active metaboli may accu and caus prolonge sedation delivered term. Hal be prolor critically i patients hepatic a renal imp Risk of de Also, it in with drug the ICU t CYP meta Injection contains propylen solvent a cannot b delivered continuo infusion. site pain

					of phlebi usefulnes injections **Role:** Sel used for of critical patients. useful fo ill patient of alcoho withdraw seizures drug ove poisonin
Antipsychotics					
Haloperidol[§]	0.03 to 0.15 mg/kg[¶] Variable doses; refer to UpToDate topics on sedative-analgesic medications in critically ill patients: properties, dose regimens, and adverse effects	0.03 to 0.15 mg/kg every 30 minutes to 6 hours Various regimens; refer to UpToDate topics on sedative-analgesic medications in critically ill patients: properties, dose regimens, and adverse effects	IV: 5 to 20	30 to 360[Δ]	**Advanta** Moderate sedating dopamin antagoni control o symptom delirium psychose Minimal cardiores effects in euvolemi hemodyr stable pa **Disadvar** Complex metaboli includes and 2D6 transforn Some exp consider metaboli active or potential neurotox life becor prolonge

					repeated administ Adverse e include d depende prolonga hypotens Interacts some cor ICU drug interfere metaboli and/or by an additi prolongi QTc. Extrapyra symptom neurolep malignar syndrom in critical **Role:** Pot treatmen agitation delirium critically i patients.
Olanzapine[¥]	Optional: 5 to 10 mg IM May repeat every two to four hours if needed (maximum total 30 mg)	Oral: Initially 5 to 10 mg once daily; increase every 24 hours as needed by 5-mg increments up to 20 mg/day	IM: 15 to 45	IM: ≥120	**Advanta** Availabili short-act formulati risk of extrapyra symptom prolonga haloperic **Disadvar** Adverse e include orthostat hypotens hyperglyc somnolen prolonga

					anticholi effects. Undergo extensive metaboli including (ie, glucuron and CYP1 transforn Half-life r prolonge hours) wi increased accumula patients older, fer nonsmok and/or in setting o or renal impairme **Role:** Pot alternati on to as-r IV halope treatmen acute agi and/or d the ICU. lowest st dose and more gra patients renal and hepatic impairme and/or o factors th predispo slowed metaboli to "Disadva above).

Quetiapine[¥]	None	Oral: Initially 50 mg every 12 hours; increase every 24 hours as needed up to 400 mg/day	Oral: 60 (initial effect); ≥24 hours (full effect)	Oral: 6 to 12 hours	**Advanta** risk of extrapyra symptom possibly l of QT prolonga haloperic **Disadvar** Requires route of administr and sche dosing du slow onse action an relatively titration s Adverse e may inclu sedation orthostat hypotens risk of QT prolonga remains. Hepatica metaboli CYP3A4 t and inact metaboli **Role:** A p choice as to as-nee haloperic treatmen agitation delirium. advanced impairme initiate w reduced titrate in incremer

Ziprasidone‡	Optional: 10 mg IM May repeat every two hours if needed (maximum 40 mg total) **or** 20 mg IM May repeat once after 4 hours if needed (maximum 40 mg total)	Oral: 20 to 40 mg orally every 12 hours	IM: 30	IM: ≥90	**Advanta** Availabili short-act formulati risk of extrapyra symptom haloperic **Disadvar** Orthosta hypotens hyperglyc QT prolo undergoe extensive metaboli hepatic n and CYP3 transforn to active inactive metaboli formulati contains cyclodext potential nephroto which ca accumula renal imp an IV for is not ava Oral form needs to in a fed s (≥500 cal reliable absorptic **Role:** A p alternati on to as-n IV halope treatmen acute agi the ICU‡.

					reductior needed ir advanced impairme Specific recomme are not a Avoid pro use of IM preparati patients renal imp due to ris accumula cyclodext additive.

Dosing information in this table is for critically ill adults who are nonobese and includes indications, dosing, duration of use, and routes of administration not listed in the US Food & Drug Administration approved product labeling. In some cases, non-weight-based initial dosing is preferred, and is shown in parentheses after weight-based dosing. For additional information for patients who are obese, refer to UpToDate topic reviews on ICU management of the obese critically ill patient.

Data provided in "Characteristics and role" on drug metabolism and the presence of active metabolite(s) are included and may be useful for assessing the potential for drug interactions and risk of drug accumulation in renal and/or hepatic organ impairment.

CYP: cytochrome P-450 metabolism; IV: intravenous; ICU: intensive care unit; HR: heart rate; MAP: mean arterial pressure; NSAIDs: nonsteroidal anti-inflammatory drugs; INR: international normalized ratio; QT: QT interval on the electrocardiogram; QTc: corrected QT interval; IM: intramuscularly.

* All doses shown are for IV administration except where otherwise noted (eg, oral or rectal acetaminophen, IM olanzapine optional initial dose).

¶ One or more loading doses may be needed. Refer to onset of action data for minimum time between redosing. Loading dose should be reduced or omitted in patients who are older, hypovolemic, having increasing vasopressor requirements, or at-risk for hemodynamic compromise.

Δ Duration of action shown is for initial dosing. Duration becomes significantly prolonged after repeated dosing or with administration as a continuous infusion due to accumulation of drug in adipose tissue.

◊ As with all opioids, tolerance may require dose escalation, and withdrawal syndrome may be precipitated upon abrupt discontinuation.

§ Dosing of haloperidol in agitated schizophrenia differs from the recommendations listed in this table for agitated delirium in the ICU and is reviewed separately. Refer to UpToDate topic reviews of

emergency management of the acutely agitated or violent patient and pharmacotherapy for acute schizophrenia.

¥ The precise role of second-generation antipsychotics in the treatment or prevention of agitated delirium in ICU is not established. Quetiapine and olanzapine recommendations and data are based on limited experience and small trial results.[1,2] Some experts start at one-quarter to one-half of doses shown and titrate gradually based upon response particularly in older adults and patients with organ dysfunction.

‡ Ziprasidone recommendations and data are based on limited experience and small trial results in treatment of undifferentiated agitation without symptoms of delirium in non-critically ill emergency department patients.[3,4] Small trial results failed to demonstrate a benefit for scheduled oral ziprasidone in prevention of delirium in a general ICU population.[5]

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Adapted from:

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2. *Lexicomp Online. Copyright © 1978-2023 Lexicomp, Inc. All Rights Reserved.*
3. *Devlin JW, Skrobik Y, Gélinas C, et al. Clinical Practice Guidelines for the Prevention and Management of Pain, Agitation/Sedation, Delirium, Immobility, and Sleep Disruption in Adult Patients in the ICU. Crit Care Med 2018; 46:e825.*

Graphic 79667 Version 43.0

Marshall CT (computed tomography) classification of traumatic brain injury

Category	Definition
Diffuse injury I (no visible pathology)	No visible intracranial pathology seen on CT scan
Diffuse injury II	Cisterns are present with midline shift of 0-5 mm and/or lesions densities present; no high or mixed density lesion >25 cm^3 may include bone fragments and foreign bodies
Diffuse injury III (swelling)	Cisterns compressed or absent with midline shift 0-5 mm; no high or mixed density lesion >25 cm^3
Diffuse injury IV (shift)	Midline shift >5 mm; no high or mixed density lesion >25 cm^3
Evacuated mass lesion V	Any lesion surgically evacuated
Non-evacuated mass lesion VI	High or mixed density lesion >25 cm^3; not surgically evacuated

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Graphic 67172 Version 11.0

Contributor Disclosures

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