BRAIN INJURY RESUSCITATION

SUMMARY

Traumatic brain injury (TBI) is the leading cause of death for all age groups in the United States, contributing to over 60% of trauma-related deaths. The primary goals of management in TBI are to minimize cerebral edema and intracranial pressure (ICP) and to optimize cerebral perfusion pressure (CPP) thereby decreasing the incidence of secondary injury.

RECOMMENDATIONS

- **Level I**
  - Maintain normal body temperature. Prevent and treat hyperthermia.
  - Institute isovolemic dehydration with hypertonic saline and mannitol. Consider resuscitating hypotensive patients with 7.5 % hypertonic saline 250 ml (4cc/kg).
  - In the absence of seizure activity, prophylactic phenytoin administration should be limited to the first seven days post-injury to reduce the incidence of post-traumatic seizures.
  - Steroids should not be used in brain injury resuscitation.
- **Level II**
  - The patient's head of bed should be elevated 30° at all times.
  - Maintain normocarbia ($PaCO_2$ 35-45 torr).
  - Intracranial pressure (ICP) monitoring is indicated in patients with:
    - Glasgow Coma Score (GCS) ≤ 8 AND an abnormal admission computed tomography (CT) scan of the head.
    - GCS ≤ 8 with a normal CT scan of the head AND unilateral or bilateral motor posturing.
  - Maintain cerebral perfusion pressure (CPP) > 60 mmHg at all times.
  - Institute mild hypothermia (body temperature 33°C-35°C) for persistent intracranial hypertension with ICP > 20 mmHg despite maximum medical management including barbiturate therapy.
- **Level III**
  - Adequate sedation using short acting agents such as propofol may be instituted.
  - When ICP exceeds 20 mmHg, maintain $PaCO_2$ between 30 and 35 torr.
  - Consider pentobarbital coma for intractable intracranial hypertension (ICP > 20 mmHg).
  - In patients < 18 years old decompressive craniectomy should be considered for intractable intracranial hypertension unresponsive to medical management.

INTRODUCTION

Based on the Monroe-Kellie Doctrine, the intracranial volume [brain (80%), cerebral spinal fluid (CSF) (10%), and cerebral blood volume (10%)] is fixed by the confines of the cranial vault. Cerebral edema, tumor, hematoma, or abscess may impinge upon the normal compartment volumes, raising intracranial pressure (ICP). Since brain tissue is capable of minimal compensation in response to abnormal intracranial lesions, CSF and cerebral blood volume compartments must decrease accordingly to

EVIDENCE DEFINITIONS

- **Class I:** Prospective randomized controlled trial.
- **Class II:** Prospective clinical study or retrospective analysis of reliable data. Includes observational, cohort, prevalence, or case control studies.
- **Class III:** Retrospective study. Includes database or registry reviews, large series of case reports, expert opinion.
- **Technology assessment:** A technology study which does not lend itself to classification in the above-mentioned format. Devices are evaluated in terms of their accuracy, reliability, therapeutic potential, or cost effectiveness.

LEVEL OF RECOMMENDATION DEFINITIONS

- **Level 1:** Convincingly justifiable based on available scientific information alone. Usually based on Class I data or strong Class II evidence if randomized testing is inappropriate. Conversely, low quality or contradictory Class I data may be insufficient to support a Level I recommendation.
- **Level 2:** Reasonably justifiable based on available scientific evidence and strongly supported by expert opinion. Usually supported by Class II data or a preponderance of Class III evidence.
- **Level 3:** Supported by available data, but scientific evidence is lacking. Generally supported by Class III data. Useful for educational purposes and in guiding future clinical research.

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minimize ICP elevations. CSF compensates by draining through the lumbar plexus and decreasing its intracranial volume. Cerebral blood volume and cerebral blood flow (CBF) are directly related to ICP and are normally closely controlled by autoregulation through a wide range of systolic blood pressures, $PaCO_2$, and PaO_2.

TBI resuscitation protocols have been demonstrated to lead to less variation in ICP and a decrease in the duration of acute episodes of intracranial hypertension (1). An evidence-based medicine algorithm for resuscitation of the brain injured patient is attached. The treatment of severe TBI is based on two principles: 1) minimizing the development of cerebral edema and elevated ICP, and 2) optimizing cerebral perfusion pressure (CPP) (CPP=MAP-ICP) in order to ensure adequate cerebral oxygen delivery.

LITERATURE REVIEW

Head of bed elevation

The treatment of any patient with TBI should begin with elevation of the head 30 degrees in an attempt to reduce cerebral edema and augment venous drainage. Elevating the head from 0 to 30 degrees has been shown to significantly lower mean ICP from 20 to 14 mmHg with no significant change in the CPP or CBF (2). In patients with suspected or documented spine injury, this is best achieved by placing the patient's bed in Reverse Trendelenburg.

Normo- vs. hypothermia

Normal body temperature should be maintained. In 2001, Clifton et al. reported the results of a large prospective randomized trial evaluating the use of hypothermia in TBI patients (3). 392 patients were randomized within 6 hours of injury to hypothermia (33° C) vs. normothermia and then rewarmed after 48 hours. Mortality was 28% in the hypothermia group and 27% in the normothermia group (p=0.79). The patients in the hypothermia group demonstrated a greater incidence of pneumonia as well as longer hospital length of stay than patients in the normothermia group. They concluded that treatment with hypothermia, with body temperature reaching 33° C is not effective in improving outcomes in patients with severe TBI. A follow-up meta-analysis performed in 2002 by Alderson et al., included 14 prospective randomized trials with 1094 patients comparing hypothermia with normothermia in TBI (4). They concluded that there is no evidence that hypothermia is beneficial in the treatment of head injury, and that, earlier, encouraging trial results have not been repeated in larger trials. Based on these randomized trials, hypothermia is not recommended as a treatment option for patients with TBI.

Hypertonic vs. isotonic resuscitation

Resuscitation using hypertonic saline (HTS) solutions results in a restoration of intravascular volume, improving tissue perfusion, while producing extravascular dehydration, decreasing tissue edema and vasospasm in critical areas such as the brain. This allows restoration of MAP and resultant improvement in CPP without the worsening in cerebral edema associated with hypotonic and isotonic solutions. The exact mechanism by which HTS acts on the injured brain has yet to be fully elucidated. In a meta-analysis of the 6 prospective randomized trials evaluating HTS for the resuscitation of hypotensive TBI, patients who received HTS were twice as likely to survive as those who received saline ($p<0.05$) (5). From 1990 to 1995, Vassar et al. performed three prospective randomized trials that compared a 250 ml bolus of 7.5% HTS to a series of alternative solutions (NS, LR, 7.5% HTS with 6% dextran) in the resuscitation of hypotensive TBI patients. They concluded that: 1) the use of HTS was safe; there were no cases of intracranial bleeding or central pontine myelinolysis in 106 patients tested; 2) hypotensive trauma patients with GCS ≤ 8 had significant improvement in survival to discharge with HTS as compared to NS or LR; and 3) dextran had no additional benefit over HTS alone (6-9).

Post-traumatic seizure prophylaxis

Several studies have shown that TBI patients with no history of seizure disorder or witnessed post-traumatic seizure activity are still at increased risk of developing post-traumatic seizures if they have one or more of the following risk factors: GCS<10, cortical contusion, depressed skull fracture, EDH, SDH, intracerebral hematoma, penetrating head wound, or seizure within 24 hours or injury (10). In these patients, seizure prophylaxis reduces the risk of seizures in the early period (up to 7 days after injury), but

does not alter late seizure occurrence (beyond 7 days). Thus, seizure prophylaxis should be discontinued after 7 days in the absence of seizure activity (11).

Steroids
Multiple prospective randomized studies have demonstrated no benefit to ICP lowering or improvement in outcome with the use of steroids in TBI patients (12-14). The Brain Trauma Foundation (BTF) recommends against the use of steroids as the standard of care for all TBI patients.

ICP monitors
The BTF recommends the use of ICP monitors as a guideline and not the standard of care. No prospective, randomized study exists comparing ICP monitoring with intervention for intracranial hypertension vs. no ICP monitoring in TBI patients with GCS ≤ 8 (15). Studies supporting ICP monitoring for TBI patients are as follows. In 1982, Narayan et al. published a sentinel study evaluating 207 TBI patients with ICP monitors with the following conclusions: 1) elevation of ICP at any stage was associated with poorer outcome; 2) patients with persistently elevated ICP refractory to therapy almost always died; 3) comatose patients with an abnormal CT scan had a 53%-63% incidence of ICH, while patients with a normal CT scan at admission had a 13% incidence of ICP elevation; and 4) ICP monitors are associated with a 6.3% infection rate and 1.4% hemorrhage rate (16). In a follow up study in 1990, Eisenberg et al. evaluated 753 TBI patients and correlated head CT scan findings with ICP measurements. They concluded that TBI patients whose initial CT scans were normal had only a 10-15% chance of developing elevated ICP (17). Although these studies indicated that ICP monitors could be omitted in TBI patients with normal initial CT scan of the head, Lobato et al. went on to show that follow up CT scans of the head are very important if no ICP monitor is placed. In their study, 1 out of 3 patients with a normal admission CT scan of the head after TBI went on to develop new pathology on the follow up CT scans performed over the next few days (18). From 1991 to 1993, three large prospective studies evaluated the effect of ICP monitors on outcome in TBI patients (19-21). All three concluded that adverse outcome and mortality rates were significantly higher in patients with ICP > 20-25 mmHg. In the study by Marshall et al., ICP > 20 mmHg was found to be highly significant in predicting adverse outcome and death ($p<0.0001$). In 1993, Ghajar et al. prospectively followed 49 patients with TBI. In the first group of 34 patients, ICP monitors and CSF drainage was undertaken for ICP > 15 mmHg, while no ICP monitors or intracranial hypertension treatment was undertaken for the second group of 15 patients. Mortality for the first group was 12% while that for the second group was 53% (22).

There is one study against ICP monitoring for TBI. In 1986, Smith, et al. reported a prospective, randomized study of 80 patients with severe head injury (GCS ≤ 8) (23). All patients were intubated and moderately hyperventilated, ICP was monitored, and CT of the head was obtained every 2 to 3 days. Group I received mannitol for ICP > 25 mmHg and pentobarbital for ICP > 35 mmHg. Group II empirically received Mannitol 0.25 gm/kg every 2 hours. The mortality in the specifically treated group was 35%, while in the empirically treated group it was 42%. Although suggesting a better outcome in Group I, the difference was not statistically significant. This study was limited by its sample size; as it would have taken 349 patients in each group (rather than about 40) to demonstrate a 10% improvement in mortality.

Cerebral perfusion pressure (CPP)
Prospective studies have identified a CPP > 60 mmHg as a resuscitation endpoint associated with improved outcome following TBI. In comparative studies, artificial attempts to maintain the CPP above 70 mmHg have been associated with an increased incidence of adult respiratory distress syndrome (ARDS) without any improvement in outcome as compared to CPP > 60 mmHg (24-25).

Hyperventilation
Modest levels of hyperventilation ($PaCO_2$ 30-35 torr) are now advocated over the more aggressive hyperventilation of years past. Prospective, randomized data comparing a $PaCO_2$ of 25 versus 35 torr demonstrated improved outcome at both 3 and 6 months in the latter group, although no difference was apparent at 1 year (26). Hyperventilation has also been shown to be the second most common cause of decreased jugular venous bulb oximetry ($SjvO_2$), a measurement analogous to mixed venous oximetry (SvO_2) (26).

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Sedation

The goal of sedative therapy in patients with TBI is to prevent secondary neuronal damage due to increases in ICP or inadequate CPP. Additionally, sedatives must not interfere with performance of a clinical neurological examination (27). Selection of drug therapy in this population is challenging as there is no one agent that is considered ideal. Propofol is a sedative-hypnotic agent that has a favorable pharmacokinetic profile and beneficial effects on cerebral metabolic rate, making it an effective drug for routine sedation as well as controlling intracranial hypertension following brain injury. Its short half-life not only allows for ease of titration, but also for rapid awakening when neurological evaluation is necessary. Propofol is eliminated by hepatic conjugation to inactive metabolites and its pharmacokinetics are not altered in the presence of renal or hepatic disease. Its beneficial effects on the cerebrovasculature are mediated via dose-dependent decreases in cerebral blood flow and metabolic rate.

Although propofol is an effective sedative in the neurotrauma population, consideration must be given to several adverse effects. First, due to potent respiratory depressant effects, patients must be mechanically ventilated prior to administration. Second, cardiovascular depressant effects occur due to reductions in preload, contractility and systemic vascular resistance, which result in a decreased mean arterial pressure. This, in turn, can lead to a decreased CPP. Finally, recent reports have documented the development of a fatal syndrome associated with high-dose propofol infusion that is characterized by metabolic acidosis, rhabdomyolysis and refractory arrhythmias. This syndrome appears to be both dose and duration dependent. Although the etiology remains unclear, consideration must be given to the lipid vehicle as well as the calcium-channel and beta-blocking properties of propofol as contributors to these adverse effects. The largest series describing propofol infusion syndrome reports that it occurs at doses greater than 83 mcg/kg/minute for greater than 24 hours (28). High-dose propofol should, therefore, be utilized with caution. Due to limited information on this syndrome in adults, a heightened awareness and consistent approach to monitoring is necessary.

CT Scan

CT scan abnormalities are infrequently found in patients with minor head injuries (GCS 15) and a loss of consciousness (6-9%), however, in patients with TBI (GCS ≤ 8) they are more much common (68%-94%) (18,21). The absence of abnormalities on CT at admission does not preclude the occurrence of raised ICP, and significant new lesions may develop in 40% of patients (18). The presence on CT scan of one or more of the following has been associated with an 84-100% chance of having an unfavorable outcome: compressed cisterns, midline shift > 5 mm, multiple unilateral or bilateral contusions, and extracerebral hematoma with swelling. (18,21).

Persistent Intracranial Hypertension (ICP > 20 mm Hg)

Shiozaki et al., in a prospective randomized trial, identified a select group of patients (severe TBI with GCS ≤ 8 and persistent ICP > 20 mm Hg), that had statistically significant improvement in mortality with mild hypothermia (34°C-35°C) when compared to normothermia. The mortality rate for the hypothermic group compared to the normothermic group was 31% and 71% respectively ($p < 0.05$) (29).

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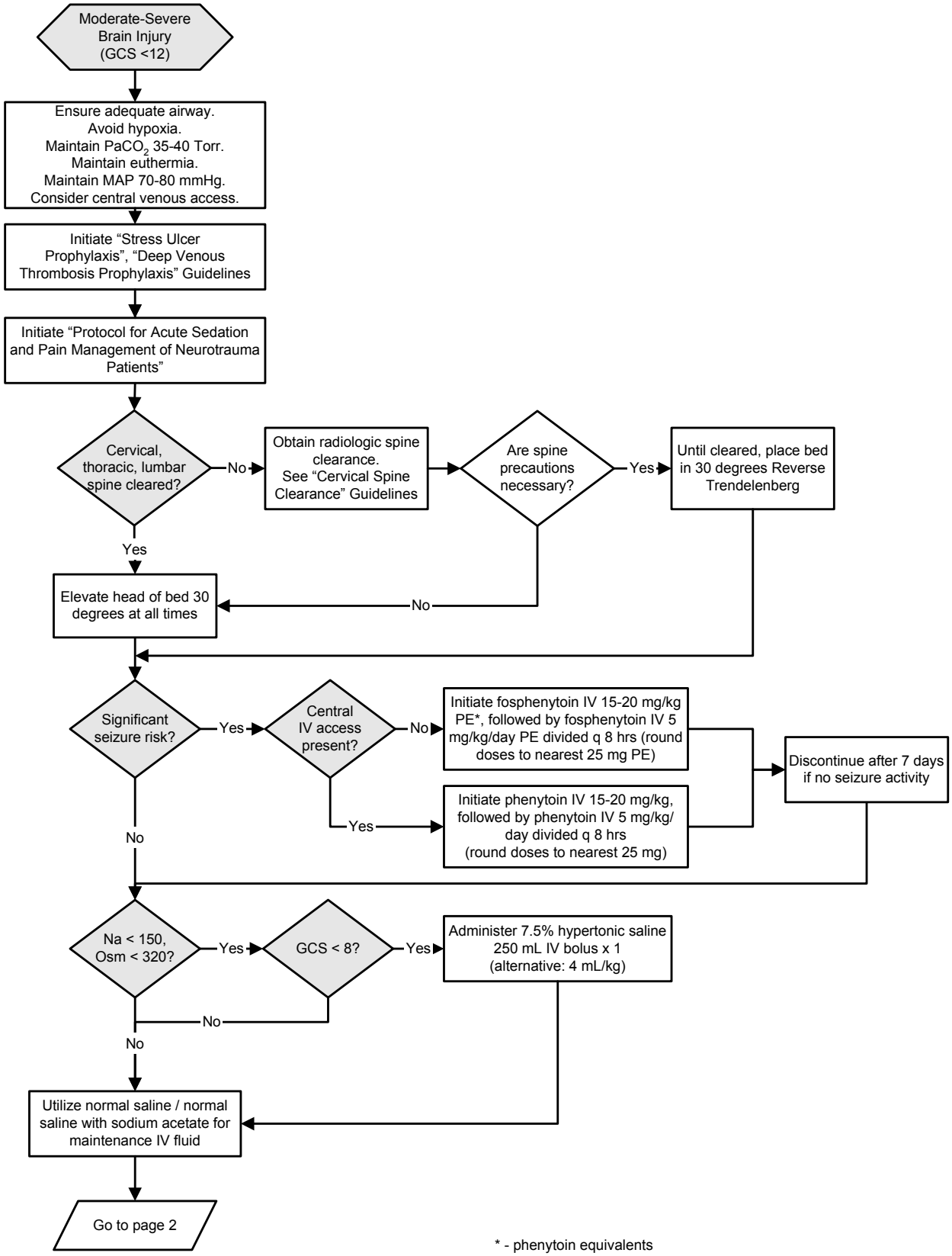
BRAIN INJURY RESUSCITATION GUIDELINES



* - phenytoin equivalents

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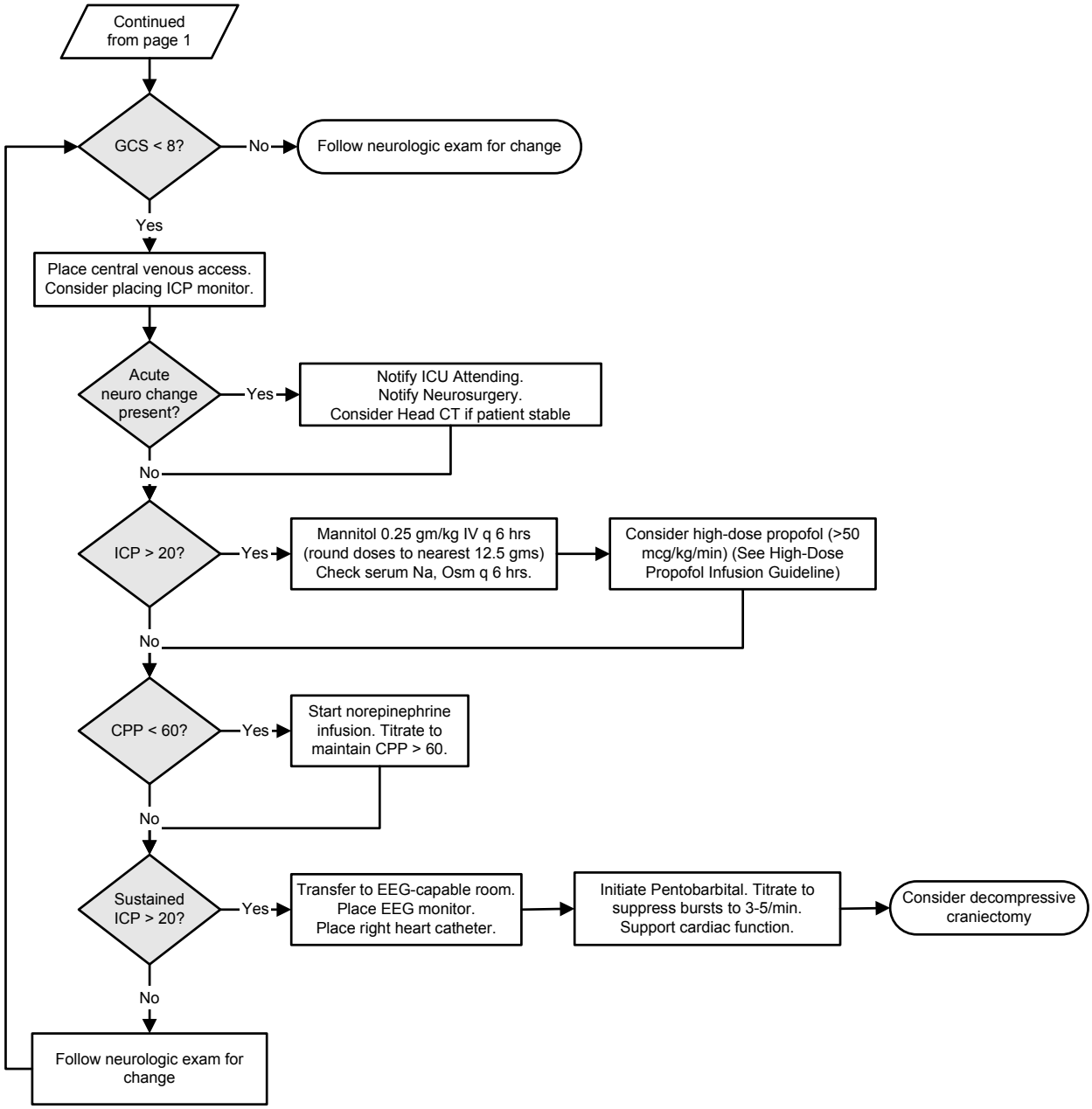

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