TRAUMATIC BRAIN INJURY GUIDELINE
Altered Mental Status in the Patient with -Traumatic Brain Injury

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I. Definition, Assessment, Diagnosis

A. Definition:

1. **Altered Mental Status (AMS)**: Alteration in level of consciousness as objectively measured by the Glasgow Coma Scale (GCS) < 15, assessing eye opening, best motor response, and verbal response (8)

2. **Level of Consciousness**: Function of the pontine reticular activating system relating to both arousal (awareness of one's surroundings) and cognition (response to various stimuli) (8)

3. **Neurologic deterioration:** Decrease in GCS score by two or more points, pupillary abnormalities (fixed unilateral or bilateral pupils, anisocoria, mydriasis, slowed/ sluggish pupil constriction), focal neurological deficits, intracranial pressure (ICP) > 20mmHg (41, 42)
   a. Depressed, i.e. confusion, lethargy, obtundation, stupor, coma
   b. Elevated, i.e. hypervigilance, agitation, insomnia, seizure

B. Assessment:

1. History:
   a. Constitutional: Fatigue, lethargy, fever, changes in appetite, unintentional weight loss or gain
   b. Head/ears/eyes/nose/throat: Headache, diplopia, vision loss, hearing loss, drooling
   c. Cardiovascular: chest pain, heart palpitations, diaphoresis
   d. Respiratory: shortness of breath, cough
   e. Gastrointestinal: constipation, diarrhea, abdominal pain, emesis
   f. Genitourinary: urinary frequency, increased urinary volume, pain with urination, sexual dysfunction
   g. Musculoskeletal: muscle or joint pain and/or swelling
   h. Integumentary: rash, acne, dry skin
   i. Neurological: mental status changes, lethargy, coma, increased tone and/or spasticity, increased muscle weakness, sensory loss, tremor, dizziness/vertigo, seizures
   j. Psychiatric: agitation, restlessness, mood lability
   k. Endocrine: temperature intolerance, changes in hair pattern and/or texture
   l. Hematologic/lymphatic: bruising, petechial lesions, bleeding
   m. History of Intracranial bleed (Subdural hematoma, epidural hematoma, subarachnoid hemorrhage, etc.)
   n. Active medication review, recent changes, over the counter supplements

2. Physical Exam:
   a. Decrease in GCS by two points and/or altered level of consciousness, either depressed or elevated
   b. Pupillary abnormalities, including fixed unilateral or bilateral pupils, anisocoria, mydriasis, slowed/ sluggish pupil constriction, papilledema, nystagmus

c. Focal neurologic signs, including cranial nerve, motor, sensory, or speech deficits
d. Flexion or extension posturing
e. Bradycardia and hypotension
f. Hyperthermia (core temperature > 38.3°C) or hypothermia (< 36°C)
g. Hypoxia
h. Abnormal respiration, increased or decreased respiratory rate
i. Seizure(s) complete or partial (see **Management of Seizures in the Patient with Traumatic Brain Injury Guideline**)
j. Altered level of consciousness, either depressed or elevated
k. New or worsening ataxia
l. New or worsening cognitive impairment
m. Tachycardia, palpitations
n. Diaphoresis
o. New or increased spasticity or muscular rigidity
p. Shivering, tremor
q. Jaundice
r. Rash with or without pruritus
s. Skin erythema, cellulitis, pain, purulent drainage

3. Laboratory test(s):
   a. Rapid glucose testing
   b. Complete blood count with differential
   c. Basic metabolic panel
   d. Urinalysis with urine culture
   e. Blood cultures
   f. Arterial blood gas (ABG)
   g. Lumbar puncture with cerebrospinal fluid (CSF) analysis
   h. Serum and urine osmolality
   i. Serum and/or urine drug levels (therapeutic and recreational drugs)
   j. Coagulation panel
   k. Thyroid function panel
   l. Liver function panel
   m. Neuroendocrine labs: adrenocorticotropic hormone (ACTH), cortisol, growth hormone, insulin-like growth factor, prolactin, gonadotrophins and sex-steroid concentrations

4. Radiologic imaging /Other:
   a. Chest x-ray: Pulmonary pathology manifestations including, aspiration, pulmonary edema, consolidation pneumonia, effusion, and opacification
   b. CT head scan without contrast: High sensitivity for demonstrating mass effect, midline shift, evidence of increased intracranial pressure, ventricular size and configuration, bone injuries, and acute hemorrhage in parenchymal, subarachnoid, subdural, or epidural spaces (7)
   c. MRI of brain: High sensitivity for detecting non-hemorrhagic primary lesions, such as contusions, infarction, diffuse axonal injury (DAI), and secondary effects of trauma such as edema (7)
   d. EEG: Capture of abnormal brain wave or epileptic activity.

C. Diagnosis
1. In patients with traumatic brain injury (TBI), AMS can be defined as neurological deterioration relative to their baseline level of consciousness

2. The common causes of AMS in TBI patients occur in the following categories:

a. **Intracranial complications**

1. Recurrent or worsening intracranial bleeding (ICB)

   a. It is estimated that 38-68% cases of traumatic hemorrhage will worsen/progress (3).

   b. A retrospective analysis of 177 initially non-operative traumatic acute subdural hematomas (SDH) found 76.8% patients had spontaneous resolution, while 23.2% required delayed surgery. Time-frame for operation was 6.8% 4 hours - 7 days, 13.6% between 7 - 28 days, and 2.8% > one month after injury (30).

   c. CT parameters predictive for delayed surgery in patients with epidural hematoma (EDH) are hematoma volume > 30cm, MLS > 5 mm, and a clot thickness > 15 mm (42).

   d. In SDH and EDH, time from neurological deterioration to surgery (significantly correlated with outcome) is more important than time between injury and surgery (no correlation with outcome). Every hour delay in surgical evacuation is associated with a progressively worse outcome (42).

   e. Of the hemorrhages, contusions are the most likely to progress (16-75% reported in literature). This typically in the first 24hours post injury but can be seen 3-4 days out (2).

2. Seizures (see **Management of Seizures in the Patient with Traumatic Brain Injury Guideline**)

3. Post Traumatic Hydrocephalus (PTH): The dilation of the ventricular system due to an imbalance between CSF production and absorption, resulting from either insufficient absorption, blockage, or overproduction of CSF and may present with elevated ICP or with normal pressure hydrocephalus (NPH) (48)

   a. Incidence in TBI reported from 11.9-86%. In severe TBI specifically it is reported as 14.2%; 25% of which were diagnosed within 2 weeks, 50% within 3 weeks, and 75% within 8 weeks of rehabilitation (12, 17).
   b. Clinical presentation is frequently atypical, and classic clinical symptoms of ICP or NPH (ataxia, urinary incontinence, and dementia) are frequently obscured.
   c. CT findings of posttraumatic ventriculomegaly can be as high as 80%. Criteria to differentiate PTH from atrophic ventriculomegaly include periventricular translucency, distended anterior horns of the lateral ventricles, enlargement of the temporal horns, and third ventricle in the presence of normal or absent sulci. However, the diagnostic specificity of these findings may not be as reliable as previously thought (49).
   d. No firm criteria for diagnosis exist. Establishing a diagnosis requires a combination of clinical deterioration or failure to improve and neuroimaging evidence of hydrocephalus.

4. Post Traumatic Infarct: (13)
   a. Incidence of acute ischemic stroke is approximately2.5% in moderate to severe TBI.

b. Risk factors include high velocity trauma and cervical dissection

c. Pharmacological complications

1. Benzodiazepines: Midazolam, lorazepam, diazepam
    a. Significant respiratory depression, sedation after drug cessation, tolerance, delirium.
    b. Abrupt withdrawal results in tremors, insomnia, and seizures.
2. Opioid narcotics: Morphine, fentanyl, etc.
    a. Ventilatory depression, sedation, hallucinations, behavioral effects, hypotension, seizures, accumulation, tolerance, and withdrawal.
    b. Prolonged infusions of opioids may hinder neurological assessment. When opioids are administered as a bolus, there is a risk of increasing the ICP, particularly when the mean arterial pressure (MAP) is allowed to fall (53).
3. Phenytoin:
    a. Shown to produce significant impairment in cognitive functions acutely (1-month post-injury) in patients with severe TBI (55)
    b. Phenytoin displays significant drug-drug interactions, has a robust side-effect profile and requires monitoring of serum drug level as toxicity is dose-dependent and frequently affects the nervous system.
4. Tricyclic antidepressants (TCA): Amitriptyline and Desipramine
    a. TCAs may be less effective in patients with TBI than in non-brain injured populations (55).
    b. Anticholinergic effects and toxicity result from peripheral blockade, and if the agent crosses the blood-brain barrier, central blockade of muscarinic acetylcholine receptors occurs. Severe cases termed *anticholinergic syndrome* may progress to coma, seizures, and respiratory depression (58).
5. Serotonin Reuptake Inhibitors (SRI): Sertraline, Fluoxetine, Paroxetine, Buspirone
    a. Serotonin toxicity occurs when there is excessive serotonergic activity in the central and peripheral nervous systems that cause the classical clinical triad of AMS, autonomic instability, and neuromuscular hyperactivity. The intensity of clinical findings reflects the degree of serotonin toxicity, termed *serotonin syndrome* when severe (57).
    b. Incidence of 18% in the exposed population.
    c. Symptoms may develop rapidly within minutes of ingestion of increased dose, addition of synergistic medication, or addition of medication that alters the hepatic metabolism of SRIs.
    d. Sertraline may lead to a decline in both motor function and cognition and an increase in the number of post-concussion symptoms reported by patients, including headache, irritability, severe akathisia, and insomnia (25).
    e. Fluoxetine's adverse effects include dysarthria and speech blocking.
    f. Buspirone's reported side effects include headache, lightheadedness, dysphoria, akathisia, agitation, irritability, angry outbursts (55), serotonin toxicity (57).
6. Lithium: adverse effects may be dose dependent (present with serum lithium levels at 1.0 meq/L , resolve when reduced to 0.5 meq/L) and can include increased cognitive impairment, irritability, agitation, neurotoxicity, increased EEG spiking (55), and serotonin toxicity (57).

7. Typical antipsychotics: Haloperidol

a. Haloperidol use in TBI patients may have negative effects on cognitive and functional performance, duration of posttraumatic amnesia, time to cognitive functioning, and behavioral deficits (54).
b. Risk of development of neuroleptic malignant syndrome (NMS), a life-threatening complication of unclear pathophysiology characterized by muscle rigidity, fever, autonomic instability, and fluctuating levels of consciousness (58)
    1. Rare complication with wide range of reported incidence rates of 0.2% to 12.2%.
    2. High fatality rate estimated at 15 – 18.8%.
    3. May progress to seizures and rhabdomyolysis, resulting in acute renal failure and multiple systemic complications, such as pneumonia, sepsis, pulmonary embolism, pulmonary edema, and cardiac arrest.

8. Atypical antipsychotics: (54) risperidone, clozapine, olanzapine, quetiapine
    b. Clozapine is associated with high adverse effect profile, including significant sedation, drooling, and seizures
    c. Also implicated in the development of NMS.

d. Infectious complications: Research suggests that catecholamines released as a result of brain injury-induced sympathetic activation to protect the brain from further inflammatory damage also modulate cells of the immune system and induce systemic immunosuppression, increasing susceptibility to infection (24).

1. The most common infectious source in TBI is urinary tract infection (UTI) with incidence of 20%, followed by pneumonia 11%, septic shock 2%, and intracranial infections 1% (14).
2. It is estimated that 23-60% of TBI patients will develop a ventilator associated pneumonia (24, 59).
3. TBI intracranial infection incidence is 12% in non-penetrating brain injury (54).

e. Metabolic or Endocrine related complications

1. **Neuroendocrine / Post-Traumatic Hypopituitarism (PTHP)**
    a. Prevalence of hypopituitarism with severe, moderate, and mild TBI (as defined by post resuscitation GCS) has been reported as 35.3%, 10.9% , and 16.8% respectively (36).
    b. Prevalence of hypopituitarism in the chronic phase after TBI is 27.5% (36).
    c. Risk factors for PTHP include raised intra-cranial pressure, long admission to the intensive care unit (ICU), diffuse axonal injury on brain imaging, and base of skull fracture (37).
    d. The diagnosis of hypopituitarism is often missed or delayed due to subtle presentation of signs and symptoms that have considerable cross-over with the sequelae of TBI i.e. fatigue, memory impairment, emotional lability, behavioral disturbance, cognitive impairment, poor motivation, and lethargy (34, 37).

2. **Adrenal Insufficiency (AI):** Damage to the anterior pituitary gland results in ACTH deficiency, causing secondary adrenal failure

a. Consequences of acute glucocorticoid deficiency after TBI are potentially fatal, resulting in life-threatening hyponatremia and hypotension requiring vasopressor support (38).
b. Incidence of ACTH deficiency within the first 2 weeks after TBI is between 4% and 78% (38).

3. **Central Diabetes Insipidus (CDI):** decreased secretion of anti-diuretic hormone (ADH) from the posterior pituitary

a. Diabetes insipidus is well recognized in the acute phase after TBI and is associated with more severe head injury, cerebral edema, and higher mortality (37).

b. Incidence in moderate to severe TBI is up to 21.6% after acute injury (36).

c. 78.4% of acute phase CDI is transient has a median onset of 6 days (range 1–9 days) and median duration of 4 days (37).

d. The hallmark of diabetes insipidus is urine volume > 3 L/day (>40-50 ml/kg every 24 h), and urine osmolality less than 300 mOsm/kg (22).

4. **Syndrome of Inappropriate Antidiuretic Hormone (SIADH) and Cerebral Salt Wasting (CSW)**
   a. SIADH and CSW are the two most common causes of hyponatremia in neurosurgery patients (21).
   b. Hyponatremia and inappropriate correction of hyponatremia is associated with a high rate of morbidity and mortality, including severe cerebral edema, mental status changes, seizures, vasospasm, osmotic demyelinating syndrome, and death (21).
   c. Median onset is 3days (1-9 days). It is almost always transient and is unrelated to the severity of the head injury (38, 39).
   d. Obtaining levels of hormones, such as ADH and natriuretic peptides, is not supported by the literature (21).
5. **Growth hormone (GH), thyroid, and gonadal axis (37)**
   a. No evidence that replacement of growth hormone, sex steroids, or thyroid hormone in the acute period is of benefit.
   b. All survivors of moderate to severe TBI should undergo screening assessment between 3 and 6 months post injury of the adrenal, thyroid and gonadal axes using the short synacthen test, baseline thyroid function tests, and gonadotrophins and sex-steroid concentrations respectively.
   c. Assessment of GH reserve at 1 year post injury using the insulin tolerance test or the glucagon stimulation test.

II. Management and Treatment Recommendations

1. Intracranial Complications:

a. Prompt recognition of neurological deterioration and appropriate clinical assessment is essential.
b. CT head scan without contrast remains the imaging modality of choice in acute neurologic deterioration (41, 46).
c. MRI is recommended for patients with acute traumatic brain injury when the neurological findings are unexplained by computed tomography and is the modality of choice for the evaluation of subacute or chronic TBI (46).

d. Other causes of AMS in TBI should be excluded without the delay of urgent neurosurgical evaluation
    1. Initial management of acute neurologic deterioration (49)
        a. Maintain hemodynamic stability with goal of systolic BP > 90-mmHg using isotonic fluid resuscitation.
        b. Continuous pulse oximetry monitoring to maintain O2 saturation > 90% or PaO2 > 60 mm Hg on ABG using supplemental oxygen
            1. Hypoxemia not corrected with supplemental O2, GCS < 9 or inability to maintain the airway warrants bag mask ventilation or rapid sequence endotracheal intubation
                a. Hypotension and hypoxemia are statistically independent predictors of outcome.
        c. Brief periods of hyperventilation therapy of 20 breaths per minute ($PaCO_2$ < 35 mmHg) should be used as a temporizing measure when clinical signs of cerebral herniation are evident by progressive neurologic deterioration, and discontinued when the clinical signs resolve.
        d. Immediate transport for CT scanning and neurosurgical evaluation.
        e. Patients with signs of progressive neurological deterioration referable to the intracranial lesion, medically refractory intracranial hypertension, or signs of mass effect on CT scan should be evaluated by a Neurosurgeon.
        f. PTH: Symptomatic hydrocephalus is indication for diversion of CSF via surgical placement of a ventriculoperitoneal shunt (17, 47).

2. **Pharmacological complications**
    a. Management and treatment include discontinuation of the offending medication and supportive treatment of symptoms.
    b. Benzodiazepines are not recommended as sleep aids in patients with TBI
    c. Serotonin toxicity (57,58)
        1. First-line management involves withdrawal of the offending serotonergic drugs and supportive care with external cooling and hydration.
            a. With sufficient treatment, mild toxicity symptoms should resolve within 24 to 72 hours
            b. Antipyretics are ineffective as hyperthermia is secondary to muscle rigidity rather than hypothalamic temperature set point
        2. Hospitalization is required in moderate to severe cases involving hypertonicity, hyperthermia, autonomic instability, or progressive cognitive changes.
        3. Benzodiazepines may be used for control of muscle rigidity, agitation and tremor.
        4. Severe hyperthermia and muscle rigidity warrant neuromuscular paralysis, sedation, and possible intubation to prevent or halt progression to rhabdomyolysis.
        5. Use of the serotonin 2A antagonist Cyproheptadine as an antidote is recommended with initial dose of 12 mg orally, followed by 2 mg every two hours until symptoms cease, and followed by maintenance dosage of 8 mg every six, hours not to exceed 0.5 mg/kg/day.
        6. An alternative, less sedating antidote is chlorpromazine hydrochloride, which is given intramuscularly at doses of 50–100 mg and repeated as necessary every 6 hours (68).
        7. Use of propranolol, bromocriptine, and dantrolene are not recommended as they may result in hypotensive shock, exacerbation of symptoms, or have no effect on survival respectively (58).
    d. Antipsychotics/Atypical Antipsychotics/NMS: (58)
        1. Immediate discontinuation of dopamine-blocking agents.
        2. Immediate initiation of supportive measures to include volume resuscitation and external cooling.

3. Benzodiazepines such as lorazepam and midazolam should be administered at doses starting at 1–2 mg intramuscularly or intravenously every four to six hours.
4. Centrally acting dopamine agonists, such as bromocriptine, levodopa, and amantadine, have been utilized successfully and are recommended in cases that fail to improve with supportive care; however, data on validity is limited.
5. In severe cases, dantrolene sodium can be used as monotherapy or in conjunction with dopamine agonists to relax skeletal muscle without causing total paralysis. It is given initially as a bolus 1.0–2.5 mg/kg and continued until signs of hypermetabolism subside or until a cumulative dose of 10 mg/kg is administered.
6. Dantrolene is continued at a dosage of 1 mg/kg every 4–6 hours for at least 24 hours to prevent the recurrence of symptoms.
7. When feasible, dantrolene is changed to oral route at a dosage of 4–8 mg/kg/day divided into four doses and continued for 1–3 days to prevent the recurrence of symptoms.
8. Common adverse effects of intravenous or intramuscular dantrolene administration are muscle weakness, phlebitis, and most seriously hepatic toxicity.
9. Symptoms typically resolve within 6–10 days after treatment is initiated.

3. **Infectious complications:**
   - **a.** Diagnosis is made in light of presenting clinical features, positive culture of the infecting organism where contamination is excluded, and /or radiological evidence of infection.
   - **b. Antimicrobial Therapy**
     1. Initial empiric anti-infective therapy is indicated in patients with sepsis to include one or more drugs that have activity against all likely pathogens (bacterial and/or fungal or viral) and that penetrate in adequate concentrations into tissues presumed to be the source of infection.
     2. Antimicrobial regimen should be reassessed daily for potential de-escalation to the most appropriate single therapy as soon as the susceptibility profile is known.
     3. Empiric combination therapy should not be administered for more than 3–5 days.
     4. Use of low procalcitonin levels or similar biomarkers can assist the clinician in the discontinuation of empiric antibiotics in patients who initially appeared septic, but who have no subsequent evidence of infection.
     5. Combination empirical therapy is used for neutropenic patients with severe sepsis and patients with multidrug resistant bacterial pathogens.
     6. Duration of therapy is typically 7–10 days; longer courses may be appropriate in patients who have a slow clinical response, undrainable foci of infection, bacteremia with S. aureus; or some fungal and viral infections or immunologic deficiencies, including neutropenia.
     7. Antiviral therapy should be initiated as early as possible in patients with severe sepsis or septic shock of viral origin.
     8. Antimicrobial agents should not be used in patients with severe inflammatory states determined to be of noninfectious cause.
   - **c. Source Control**
     1. A specific anatomical diagnosis of infection requiring consideration for emergent source control must be sought and diagnosed or excluded as rapidly as possible, and intervention must be undertaken for source control within the first 12 hr. after the diagnosis is made.
     2. When source control in a severely septic patient is required, the effective intervention associated with the least physiologic insult should be used (e.g., percutaneous rather than surgical drainage of an abscess).
     3. If intravascular access devices are a possible source of sepsis, they should be removed promptly after other vascular access has been established.
   - **d. Infection Prevention**

1. Oral chlorhexidine gluconate can be used as a form of oropharyngeal decontamination to reduce the risk of ventilator-associated pneumonia in ICU patients with severe sepsis.
2. Peri-procedural antibiotics for intubation should be administered to reduce the incidence of pneumonia (41).
3. In acute TBI, early tracheostomy should be performed to reduce mechanical ventilation days (41).
4. Ventriculostomies and other ICP monitors should be placed under sterile conditions to closed drainage systems, minimizing manipulation and flushing. Routine ventricular catheter exchange or prophylactic antibiotic use for ventricular catheter placement is not recommended to reduce CSF infections (41).
5. There is no support for the use of antibiotics for systemic prophylaxis longer than 48 hours in intubated TBI patients given the risk of selecting for resistant organisms (41).

4. **Endocrine and metabolic complications**
   a. **Adrenal insufficiency (AI)**
      1. Closely monitor signs and symptoms of hypocortisolism, including hyponatremia, hypotension resistant to inotropes, hypoglycemia, or unexpected slow recovery (36).
      2. During the acute phase (Days 1-7) of moderate to severe brain injury, it warrants daily monitoring of morning serum cortisol levels. Measurement of less than 7.2 µg/dL (200 nmol/L) are suggestive of adrenal insufficiency and stress dose glucocorticoid replacement should be instituted. Values between 7.2 and 18 µg/dL (200-500 nmol/L) in the presence of AI features may still be inappropriately low, and a trial of glucocortioid therapy should be considered (36).
      3. During the chronic phase (> 2 weeks): The insulin tolerance test is considered the criterion standard for assessing the growth hormone and the adrenal axes. It is contraindicated in acute TBI and in patients with severe cardiovascular disease and uncontrolled epileptic seizures. In such cases, the use of the glucagon test confirmed with the short synacthen test is utilized (36).
      4. Persistent/chronic hypocortisolemia warrants hormone replacement treatment with standard oral maintenance dose (36,38).
   b. **Central diabetes insipidus**
      1. Acute phase CDI: hypotonic polyuria associated with presence of hypernatremia and /or elevated plasma osmolality warrants trial of injection subcutaneously or intravenously of 1 µg of 1-deamino-8-D-arginine vasopressin (DDAVP). A greater than 50% increase in urine osmolality measurement in 1-2hours confirms the diagnosis (22).
      2. Chronic phase CDI is formally evaluated using a standard 8-hour water deprivation test, followed by desmopressin challenge (38).
      3. Acute phase CDI warrants immediate hormone replacement therapy with desmopressin (subcutaneously or intramuscularly) and hypotonic fluids guided by the urine output and the plasma sodium (37).
      4. Chronic phase CDI is maintained with oral desmopressin (38).

   c. **SIADH/CSW**
      1. Acute symptomatic hyponatremia (<48 hours): Correction with hypertonic saline (3 %) to raise plasma sodium by 1–2 mmol/h to a total of 4–6 mmol to alleviate signs and symptoms, followed by chronic correction guidelines (40).
      2. Chronic (> 48 hours) hyponatremia: Correction should be no faster than 0.5 mmol/h to avoid the risk of osmotic demyelination syndrome (40).

III. Prevention and Education

A. Education of the caregiver and patient on common complications after traumatic brain injury is essential in early detection of intracranial, pharmacological, infectious, metabolic , and endocrine -related complications that may result in altered mental status.

B. Use the smallest effective dose of medications for management of pain, spasticity, mood/behavioral issues, and seizures.
C. Routine follow up with a medical team familiar with metabolic and endocrine issues that may occur after TBI is important for monitoring and early detection of complications.

This guideline was developed to improve health care access in Arkansas and to aid health care providers in making decisions about appropriate patient care. The needs of the individual patient, resources available, and limitations unique to the institution or type of practice may warrant variations.

Guideline Developers

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