# TRIUMPH Call Center TBI Guidelines Altered Mental Status in Patients with Traumatic Brain Injury

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## I. Definition, Assessment, Diagnosis

- **3. Neurologic deterioration:** Decrease in GCS score by two or more points, pupillary abnormalities (fixed unilateral or bilateral pupils, anisocoria, mydriasis, slowed/ sluggish constriction), focal neurological deficits, Intracranial Pressure (ICP) > 20mmHg (Brain Trauma Foundation 43, 44)
  - **Depressed** i.e. confusion, lethargy, obtundation, stupor, coma
  - **Elevated** i.e hypervigilence, agitation, insomnia, seizure

## Altered Mental Status in Patients with Traumatic Brain Injury

**I. Definition, Assessment, Diagnosis**

- **1. Altered Mental Status (AMS):** Alteration in level of consciousness as objectively measured by 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)

## Assessment:

1. History:

- Constitutional: Fatigue, lethargy, fever, changes in appetite, unintentional weight loss or gain
- Head/ears/eyes/nose/throat: Headache, diplopia, vision loss, hearing loss, drooling
- Cardiovascular: chest pain, heart palpitations, diaphoresis
- Respiratory: shortness of breath, cough
- Gastrointestinal: constipation, diarrhea, abdominal pain, emesis
- Genitourinary: urinary frequency, increased urinary volume, pain with urination, sexual dysfunction
- Musculoskeletal: muscle or joint pain and/or swelling
- Integumentary: rash, acne, dry skin
- Neurological: mental status changes, lethargy, coma, increased tone and/or spasticity, increased muscle weakness, sensory loss, tremor, dizziness/vertigo, seizures
- Psychiatric: agitation, restlessness, mood lability
- Endocrine: temperature intolerance, changes in hair pattern and/or texture
- Hematologic/lymphatic: bruising, petechial lesions, bleeding
- History of Intracranial bleed (Subdural hematoma, epidural hematoma, subarachnoid hemorrhage, etc)
- Medication list review, additions, dose changes, and supplements

## Assessment:

### 2. Physical Exam:

- Decrease in GCS by two points and/or altered level of consciousness either depressed or elevated
- Pupillary abnormalities including fixed unilateral or bilateral pupils, anisocoria, mydriasis, slowed/ sluggish constriction, papilledema, nystagmus
- Focal neurologic signs including cranial nerve, motor, sensory, or speech deficits
- Flexion or extension posturing
- Bradycardia and hypotension
- Hyperthermia
- Hypoxia
- Abnormal respiration, decreased breath sounds on lung examination
- Observed seizure(s): complete or partial (see Post Traumatic Seizure Guideline)
- Altered level of consciousness either depressed or elevated
- New or worsening ataxia
- New or worsening cognitive impairment
- Tachycardia, palpitations
- Diaphoresis
- New or increased spasticity or muscular rigidity
- Shivering, tremor
- Jaundice
- General: Fever (> 38.3°C), Hypothermia (core temperature < 36°C
- Skin erythema, cellulitis, pain, and purulent drainage, rash with or without pruritus

## Assessment:

### 3. Laboratory test:

- Complete blood count with differential
- Basic metabolic panel
- Urinalysis with urine culture
- Blood cultures
- Lumbar puncture with CSF analysis
- Serum and Urine osmolality
- Serum and/or urine drug levels (therapeutic and recreational drugs)
- Coagulation panel: PT/PTT/INR
- Thyroid function panel
- Liver function panel
- Neuroendocrine labs: prolactin, growth hormone, testosterone, insulin-like growth factor, cortisol, ACTH

## Assessment:

### 4. Radiologic imaging /Other:

- Chest Xray: pulmonary pathology manifestations including aspiration, pulmonary edema, consolidation pneumonia, effusion, and opacification.
- CT head without contrast: High sensitivity for demonstrating mass effect, midline shift, evidence of increased intracranial pressure, ventricular size and configuration, and acute hemorrhage in parenchymal, subarachnoid, subdural, or epidural spaces (7)
- MRI brain: High sensitivity for detecting non-hemorrhagic primary lesions such as contusions, infarction, DAI and secondary effects of trauma such as edema. (7)
- Electroencephalogram (EEG): capture of epileptic activity.

## Diagnosis:

In patients with TBI, altered mental status can be defined as neurological deterioration relative to their baseline level of consciousness

Differential diagnosis for AMS in TBI patients

## a. Intracranial complications:

- **1. Recurrent or worsening intracranial bleeding (ICB):**
  - Incidence of 4.8% in mTBI (3) 5.2% had progression on repeat CT (4) No patients had neurological deterioration (3,4)
  - 23.2% Initially non-operative traumatic acute Subdural Hematomas 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)
  - Time from neurological deterioration to surgery (significantly correlated with outcome) whereas no outcome correlation was found between time of injury and surgery (44)
  - 45% of patients with brain contusions have radiologically significant progression and 19% require surgical intervention. Time frame for deterioration 5 hours – 4 days (2)
- **2. Seizures** (See Post Traumatic Seizures in TBI Guidelines)

Differential diagnosis for AMS in TBI patients

## a. Intracranial complications:

- **4. Post Traumatic Infarct:**
  - Incidence of 11.96% in moderate to severe TBI
  - 30.95% Occur within the first week in, 42.86% 8 days to 2 weeks, 14.29% 2 to 3 weeks in, 7.14%, 3 weeks to 1 month in and 1 to 3 months in 4.76%
  - Significant risk factors are low GCS, low systolic BP, brain herniation, and decompression craniotomy

Differential diagnosis for AMS in TBI patients

## a. Intracranial complications:

- **3. Post Traumatic Hydrocephalus:** The dilation of the ventricular system due to an imbalance between Cerebrospinal Fluid (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) (50)
  - Incidence in severe TBI is 14.2%; 25% were diagnosed within 2 weeks, 50% within 3 weeks, and 75% within 8 weeks (19)
  - Incidence status post decompressive craniotomy is 34.5% occurring both before and after cranioplasty with the only significant independent risk factor is craniotomy with superior limit <25mm from the midline (13)
  - CT findings of posttraumatic ventriculomegaly can be as high as 80%. Criteria exists to differentiate PTH from atrophic ventriculomegaly including enlargement of the temporal horns and third ventricle in the presence of normal or absent sulci (51)
  - Diagnosis requires a combination of clinical deterioration or failure to improve and neuroimaging evidence of hydrocephalus

Differential diagnosis for AMS in TBI patients

## b. Pharmacologic complications:

- Benzodiazepines: Midazolam, lorazepam, diazepam
  - Significant respiratory depression, prolonged sedation after drug cessation, tolerance, delirium
  - Abrupt withdrawal results in tremors, insomnia and seizures
- Barbiturates: Pentobarbital, thiopetone
  - Long half life results in accumulation resulting in prolonged sedation precluding neurological assessment for several days
- Opioid narcotics: Morphine, fentanyl, etc.
  - Ventilatory depression, sedation, hallucinations, behavioral effects, seizures, accumulation, tolerance, withdrawal, and risk of increase in ICP

Differential diagnosis for AMS in TBI patients

## b. Pharmacologic complications:

- Phenytoin:
  - Shown to produce significant impairment in cognitive functions acutely (1 month post-injury) in patients with severe TBI (57)
  - Phenytoin toxicity is dose dependent and results in nystagmus, nausea and vomiting, ataxia, and CNS depression

Differential diagnosis for AMS in TBI patients

## b. Pharmacologic complications:

- Serotonin Reuptake Inhibitors (SRI): Sertraline, Fluoxetine, Paroxetine, Buspirone
  - Serotonin toxicity(59): excessive serotonergic activity in the central and peripheral nervous systems causing 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
  - Incidence of 18% in the exposed population
  - Symptoms may develop rapidly within minutes of ingestion of increased dose, addition of synergistic medication, or addition of medication that alter hepatic metabolism of SRIs

Differential diagnosis for AMS in TBI patients **b.**

## Pharmacologic complications:

- Tricyclic antidepressants (TCA): Amitriptyline and Desipramine
  - TCAs may be less effective in patients with TBI than in non-brain injured populations (57)
  - Anticholinergic effects and toxicity result from peripheral and if the agent crosses the blood brain barrier central blockade of muscarinic acetylcholine receptors where severe cases termed anticholinergic syndrome may progress to coma, seizures, and respiratory depression (60)
- Lithium:
  - Adverse effects include increased cognitive impairment, irritability, agitation, neurotoxicity, increased EEG spiking (57), and serotonin toxicity (59)
  - Adverse effects may be dose dependent (present with serum lithium levels at 1.0 meq/L , resolve when reduced to 0.5 meq/L) (57)

Differential diagnosis for AMS in TBI patients

## b. Pharmacological complications:

- Sertraline may lead to a decline in both motor function and cognition and an increase in the number of postconcussion symptoms reported by patients including headache, irritability, severe akathisia and insomnia (27)
- Fluoxetine adverse effects include dysarthria and speech blocking
- Buspirone side effects include headache, lightheadedness, dysphoria, restlessness consistent with post-traumatic akathisia, agitation, irritability, angry outbursts (57), serotonin toxicity (59)

Differential diagnosis for AMS in TBI patients

## b. Pharmacologic complications:

- Typical antipsychotics: Haloperidol
  - 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 (56)
  - 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 (60)
    - Rare complication with wide range of reported incidence 0.2% to 12.2%
    - High fatality rate estimated at 15 – 18.8%
    - 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

Differential diagnosis for AMS in TBI patients

## c. 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 (26)

Differential diagnosis for AMS in TBI patients

## b. Pharmacologic complications:

- Atypical antipsychotics: (56) risperidone, clozapine, olanzapine, quetiapine
  - clozapine is associated with high adverse effect profile including significant sedation, drooling, and seizures
  - Also implicated in the development of NMS

Differential diagnosis for AMS in TBI patients

## c. Infectious complications:

- The overall most common infectious source in TBI is urinary tract infection (UTI) with incidence of 20% followed by pneumonia 11%, septic shock 2% and 1% intracranial infections (16)
- Approximately 50% of patients with severe TBI develop at least one infectious complication during hospitalization with pneumonia being the most frequent with incidence ranging between 41% and 74% (26)

Differential diagnosis for AMS in TBI patients

## d. Metabolic or Endocrine complications:

- **1. Endocrine / Glycemic control:**
  - Diabetes Mellitus (DM) is associated with 1.5-fold increase in mortality compared to non diabetics after sustaining isolated TBI (9) The increase is significant independent of age-related DM comorbidities (11)
  - Avoiding insulin deficiency, as well as hypoglycemia, may reduce mortality in TBI patients (11)

Differential diagnosis for AMS in TBI patients

## d. Metabolic or Endocrine complications:

- **3. Neuroendocrine / Post-Traumatic Hypopituitarism (PTHP)**
  - Large neuropathological studies have demonstrated different types of traumatic pituitary lesions including damage to the pituitary capsule, injury to the anterior and/or posterior lobes and pituitary stalk in the form of hemorrhage, infarction, necrosis, and fibrosis (38)
  - Prevalence of hypopituitarism with severe, moderate, and mild were 35.3%, 10.9% , and 16.8% respectively (38)
  - Prevalence of hypopituitarism in the chronic phase after TBI 27.5% (38)
  - Risk factors for PTHP include raised ICP, long ICU stay, DAI, and base of skull fracture (39)

Differential diagnosis for AMS in TBI patients

## d. Metabolic or Endocrine complications:

- **2. Adrenal Insufficiency (AI):** Damage to the anterior pituitary gland results in ACTH deficiency causing secondary adrenal failure
  - Consequences of acute glucocorticoid deficiency after TBI are potentially fatal, resulting in life-threatening hyponatremia and hypotension requiring vasopressor support (40)
  - Incidence of ACTH deficiency within the first 2 weeks after TBI between 4% and 78% (40)

Differential diagnosis for AMS in TBI patients

## d. Metabolic or Endocrine complications:

**Growth Hormone, thyroid, gonadal axis:**

- No evidence that replacement of growth hormone, sex steroids or thyroid hormone in the acute period is of benefit (39)
- All survivors of moderate to severe TBI should undergo screening assessment between 3 and 6 months of the adrenal, thyroid and gonadal axes using the short synacthen test, baseline thyroid function tests, gonadotrophins and sex-steroid concentrations respectively
- Assessment of growth hormone (GH) reserve at 1 year using the insulin tolerance test (ITT) or the glucagon stimulation test (39)

Differential diagnosis for AMS in TBI patients

## d. Metabolic or Endocrine complications:

- The diagnosis of hypopituitarism is often missed or delayed with potentially serious and life-threatening consequences (38) likely 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 (39)

Differential diagnosis for AMS in TBI patients

## d. Metabolic or Endocrine complications:

- **5. Syndrome of Inappropriate Antidiuretic Hormone (SIADH) and Cerebral Salt Wasting (CSW):**
  - The two most common causes of hyponatremia in neurosurgery patients (23)
  - Hyponatremia and inappropriate correction of hyponatremia is associated with high rate of morbidity and mortality including severe cerebral edema, mental status changes, seizures, vasospasm, osmotic demyelinating syndrome and death (23)
  - Median onset is 3 (1-9 days). It is almost always transient and is unrelated to the severity of the head injury (40,41)
  - Obtaining hormone levels of ADH and natriuretic peptides is not supported by the literature (23)

Differential diagnosis for AMS in TBI patients

## d. Metabolic or Endocrine complications:

- **4. Central Diabetes Insipidus (CDI):** decreased secretion of Anti-Diuretic Hormone from the posterior pituitary
  - Diabetes insipidus is well recognized in the acute phase after TBI, and is associated with higher severity head injury, cerebral edema, and higher mortality (40)
  - Incidence in moderate to severe TBI of up to 26% in the acute phase and 7% in long-term survivors (39)
  - 78.4% of acute phase CDI is transient. Median onset is 6 days (range 1–9 days) with median duration of 4 days (40)
  - The hallmark of DI is urine volume > 3 L/day (>40-50 ml/kg every 24 h), and urine osmolality is less than 300 mOsm/kg (24)

## II. Management and Treatment Recommendations

## a. Intracranial Complications:

- Prompt recognition of neurological deterioration and appropriate clinical assessment is essential
- CT head without contrast remains the imaging modality of choice in acute neurologic deterioration with the most studied diagnostic and prognostic criteria (44, 49)
- MRI is recommended for patients with acute traumatic brain injury when the neurological findings are unexplained by CT and is the modality of choice for the evaluation of subacute or chronic TBI (49)
- Other causes of AMS in TBI should be excluded without the delay of urgent neurosurgical evaluation

## II. Management and Treatment Recommendations a. Intracranial Complications:

- Initial management of acute neurologic deterioration: (52)
  - Maintain hemodynamic stability with goal of systolic BP > 90-mmHg using isotonic fluid resuscitation
  - Continuous pulse oximetry monitoring to maintain O2 saturation > 90% or PaO2 > 60 mm Hg on ABG using supplemental oxygen
    - Hypoxemia not corrected with supplemental O2, GCS < 9 or inability to maintain the airway warrants bag mask ventilation or rapid sequence endotracheal intubation
    - Hypotension and hypoxemia are statistically independent predictors of outcome due to effect on oxygen delivery and Cerebral Perfusion Pressure [(CPP) = Mean arterial pressure – ICP] and subsequent secondary insult
  - 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
  - Patients with signs of progressive neurological deterioration referable to the intracranial lesion, medically refractory ICH, or signs of mass effect on CT scan warrant immediate Neurosurgical evaluation
  - PTH: Symptomatic hydrocephalus is indication for diversion of CSF via surgical placement of a ventriculoperitoneal shunt (19,50)

## II. Management and Treatment Recommendations b. Pharmacologic Complications:

- **Serotonin toxicity: (59,60)**
  - First line management involves withdrawal of the offending serotonergic drugs and supportive care with external cooling and hydration
    - With sufficient for treatment of mild toxicity symptoms should resolve within 24 to 72 hours
    - Antipyretics are ineffective as hyperthermia is secondary to muscle rigidity rather than hypothalamic temperature set point
  - Hospitalization is required in moderate to severe cases involving hypertonicity, hyperthermia, autonomic instability, or progressive cognitive changes
  - Benzodiazepines may be used for control of muscle rigidity, agitation and tremor
  - Severe hyperthermia and muscle rigidity warrant neuromuscular paralysis, sedation, and possible intubation to prevent or halt progression to rhabdomyolysis
  - 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 followed by maintenance dose of 8 mg every six hours not to exceed 0.5 mg/kg/day
  - Alternate less sedating antidote is chlorpromazine hydrochloride given intramuscularly at doses of 50–100 mg, repeated as necessary every 6 hours (60)
  - 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 (60

## II. Management and Treatment Recommendations b. Pharmacologic Complications:

- Management and treatment include immediate discontinuation or tapering of the offending medication and supportive treatment of symptoms

## II. Management and Treatment Recommendations b. Pharmacologic Complications:

- **Antipsychotics/Atypical Antipsychotics/NMS: (60)**
  - Immediate discontinuation of dopamine-blocking agents upon diagnosis
  - Immediate initiation of supportive measures to include volume resuscitation and external cooling
  - Benzodiazepines such as lorazepam and midazolam administered at doses starting of 1–2 mg intramuscularly or intravenously every four to six hours
  - 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
  - In severe cases dantrolene sodium can be used as monotherapy or in conjunction with dopamine agonists to relax skeletal muscle without causing total paralysis 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
  - 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
  - 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
  - Common adverse effects of intravenous or intramuscular dantrolene administration are muscle weakness, phlebitis and most seriously hepatic toxicity
  - Symptoms typically resolve within 6–10 days after treatment is initiated

## II. Management and Treatment Recommendations b. Infectious Complications:

- 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
- **Antimicrobial Therapy**
  - Initial empiric anti-infective therapy is indicated in patients with sepsis to include one or more drugs that have activity against all likely pathogens and adequate penetration into source tissues
  - Antimicrobial regimen should be reassessed daily for potential deescalation to the most appropriate single therapy as soon as the susceptibility profile is known
  - Empiric combination therapy should not be administered for more than 3–5 days
  - Use of low procalcitonin levels or similar biomarkers to assist in the discontinuation of empiric antibiotics in patients who have no subsequent evidence of infection
  - Duration of therapy 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;* some fungal and viral infections or immunologic deficiencies,
  - Antimicrobial agents should not be used in patients with severe inflammatory states determined to be of noninfectious cause

## II. Management and Treatment Recommendations b. Infectious Complications:

- **Infection Prevention**
  - Oral chlorhexidine gluconate be used as a form of oropharyngeal decontamination to reduce the risk of ventilator-associated pneumonia in ICU patients with severe sepsis
  - Peri-procedural antibiotics for intubation should be administered to reduce incidence of pneumonia (43)
  - In acute TBI, Early tracheostomy should be performed to reduce mechanical ventilation days (43)
  - 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 (43)
  - There is no support for use of antibiotics for systemic prophylaxis for longer than 48 hours in intubated TBI patients given the risk of selecting for resistant organisms (43)

## II. Management and Treatment Recommendations b. Infectious Complications:

- **Source Control**
  - A specific anatomical diagnosis of infection requiring consideration for emergent source control be sought and diagnosed or excluded as rapidly as possible, and intervention be undertaken for source control within the first 12 hr after the diagnosis is made
  - When source control in a severely septic patient is required, the effective intervention associated with the least physiologic insult should be used (eg, percutaneous rather than surgical drainage)
  - If intravascular access devices are a possible source of sepsis, they should be removed promptly after other vascular access has been established

## II. Management and Treatment Recommendations b. Endocrine and Metabolic Complications:

- Hyperglycemia:
  - STAT Rapid blood glucose measurement
  - Routine monitoring Q4H or AC&HS in diabetic patients
  - Intensive Insulin Therapy aimed to maintain strict normoglycemia remains controversial as it has not shown benefit in mortality or neurological outcome compared to conventional glycemic control while significantly increasing the risk of hypoglycemic episodes (36,37)
  - Correction with low to moderate sliding scale insulin therapy and hypoglycemic protocol are both safe and effective

## II. Management and Treatment Recommendations
## b. Endocrine and Metabolic Complications:

- **Adrenal Insufficiency (AI):**
  - Close monitoring of signs and symptoms of hypocortisolism including hyponatremia, hypotension resistant to inotropes, hypoglycemia, or unexpected slow recovery (38)
  - Acute phase (Days 1-7) of moderate to severe brain injury: daily monitoring of morning serum cortisol level. 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 (38)
  - 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, 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. (38).
  - Persistent/chronic hypocortisolemia warrants hormone replacement treatment with standard oral maintenance dose (38,40)

## III. Prevention and Education

- 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
- Use the smallest effective dose of medications for management of pain, spasticity, mood/behavioral issues, and seizures
- 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

## II. Management and Treatment Recommendations
## b. Endocrine and Metabolic Complications:

- **Central Diabetes Insipidus (CDI):**
  - 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). >50% increase in urine osmolality measurement in 1-2hours confirms the diagnosis(24)
  - Chronic phase CDI is formally evaluated using a standard 8-hour water deprivation test followed by desmopressin challenge (40)
  - 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 (39)
  - Chronic phase CDI is maintained with oral desmopressin (40)
- **SIADH/CSW:**
  - 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 (42)
  - Chronic (> 48 hours) hyponatremia: Correction should be no faster than 0.5 mmol/h to avoid the risk of osmotic demyelination syndrome (42)

## References: