Electrolyte Disturbances in brain deathPatients

Presented by:
Dr.Y.Haghdar saheli
Assistant Professor of GUMS

- Every day, the demand for organs is increasing at a faster rate than that at which organs are becoming available for transplants.

- With this increasing demand, the responsibility with regard to caring for potential organ donors is also rising.

- Appropriate medical management of a potential organ donor is a very important issue, requiring a multidisciplinary team approach for successful organ transplantation

- A potential organ donor is defined by the presence of either brain death or a catastrophic and irreversible brain injury that leads to fulfilling the brain death criteria .

- Brain death is defined as the irreversible loss of all brain functions, including the brain stem.

- Brain death occurs in response to increased intracranial volume, which may be caused by brain swelling and the collection or obstruction of cerebrospinal fluid flow (hydrocephalus) . As the intracranial pressure (ICP) rises, blood flow to the brain falls and finally stops: the brain dies=irreversible=patient death

PATHOPHYSIOLOGICAL CHANGES IN IRREVERSIBLE LOSS OF BRAIN FUNCTION

- Different clinical studies have shown that central sympathoadrenergic regulation of circulation and the pituitary temperature are disrupted during development and irreversible loss of brain function; thus, there is an interruption in hypothalamic-pituitary-adrenocortical regulation .
- The rising ICP results in a massive release of proinflammatory and anti-inflammatory cytokines and catecholamines .
- Ultimately, brain death results in the loss of central regulatory mechanisms, which leads to several pathophysiological alterations in hemodynamics, hormone balance, body temperature, and lung function

Table 1. Frequency of pathophysiological changes in irreversible loss of brain function

Variable	Cause	Frequency (%)
Hypothermia	Hypothalamic dysfunction, vasoplegia	100
Hypotension	Vasoplegia, hypovolemia, myocardial dysfunction	80–97
Diabetes insipidus	Hypothalamic/pituitary dysfunction	65–90
Arrhythmias	Catecholamine release, myocardial injury	25–32
Pulmonary edema	Injury to vascular endothelium	15–20
Cardiac arrest	Prolonged hypotension, arrhythmia	5–10

Cardiovascular Changes

- In a brain-dead patient, ICP rises, which compromises cerebral blood flow and causes hemodynamic changes, described as the “Cushing reflex,” which is a mixed picture of vagal and sympathetic stimulation. As pontine ischemia develops, it clinically manifests as bradycardia and hypertension .

- When blood supply is further compromised, ischemia progresses to the medulla oblongata, involving the vagal motor nucleus. This results in compensatory arterial hypertension, perhaps associated with bradycardia, followed by marked sympathetic stimulation with intense vasoconstriction, raised systemic vascular resistance, and tachycardia . This clinical picture is known as the “catecholamine storm,” and these features are also associated with central redistribution of blood volume, increased afterload, and visceral ischemia .

- As ischemia progress down the spinal cord, it may cause loss of function in the thoracic sympathetic chain with severe hypotension resulting from a reduction in afterload.
- As the aortic diastolic pressure decreases, it may compromise the coronary perfusion pressure to critical levels, resulting in myocardial ischemia .
- The resulting hypotension may lead to hypoperfusion of all organs, including the heart, if not properly and timely treated, and may contribute to rapid donor loss .
- Additional factors may contribute to hypotension, including diuretics (mannitol), hyperglycemia-induced osmotic diuresis diabetes insipidus (DI), hypothermic “cold” diuresis, inadequate fluid resuscitation and decreased oncotic pressure after crystalloid resuscitation, ongoing blood loss, rewarming of the patient, and relative adrenal insufficiency as a result of trauma, and critical illnesses

Respiratory Changes

- The lungs are the organs most often assumed to be medically unsuitable for transplants, with only 10%–20% of lungs eligible for transplantation . Neurogenic pulmonary edema (NPE) and inflammatory acute lung injury are the two main factors related to brain-death-induced lung injury and dysfunction .
- In a brain-dead person, the NPE is related to a sympathetic storm caused by hemodynamic and sympathetic mechanisms. NPE can occur immediately after a neurological insult, but it may also occur earlier, before the patient is distinguished as a potential organ donor .

- This elevated hydrostatic pressure would ultimately lead to structural damage to the capillary endothelium . Respiratory arrhythmias may progress to apnea and cardiac arrest if there is no supporting mechanical ventilation

- In addition, proinflammatory mediators that are released following brain death may further contribute toward lung injury by promoting infiltration of activated neutrophils into the lungs

- Other contributing factors for lung dysfunction include chest trauma, aspiration, and atelectasis .
- Moreover, long-term dependency on mechanical ventilation also creates a predisposition toward nosocomial chest infections

Renal Changes

- Experimental models have demonstrated that biomarkers for renal tubular injuries may be elevated as early as 30 minutes after the onset of brain death .
- Both proinflammatory and procoagulant effects caused by brain death have been identified as main contributing factors .
- Pretransplant kidney biopsies of a brain-dead donor found that the kidneys contain more infiltrating T lymphocytes and macrophages compared to those from living and cardiac-dead donors.
- There is also compelling evidence showing a greater release of inflammatory cytokines during reperfusions in brain-dead donor kidneys

- Dyselectrolytemia is very common in head injuries patients and it is likely due to abnormality in serum sodium, potassium, calcium, phosphate.
- It may be due to use of intravenous fluids, diuretics, SIADH secretion and cerebral salt washing.
- Serum Sodium is the most common and important electrolyte abnormality responsible among these electrolytes.
- Both hyponatremia and hypernatremia can result.

- There are some different causes and among them most common being SIADH , Cerebral salt wasting (CSW) , use of diuretics like Furosemide and Mannitol.
- Age is another important factor that also greatly affects morbidity and mortality. Advancing age has poor outcome appropriate fluid management of patients with brain injury.
- Apart from Sodium and Potassium, Serum calcium is also is important electrolyte abnormality associated with a variety of clinical manifestations in patients with brain injury.

Endocrine Changes

- Brain death may cause significant endocrine changes that vary in timing and severity, resulting in anterior and posterior pituitary failure .
- Animal studies have shown that in baboons with acute increases in ICP, posterior and anterior pituitary function is rapidly lost after brain death , which is associated with deterioration in cardiac function and a shift to an anaerobic metabolism. However, the profile is less consistent in the case of human donors .

- Function of the posterior pituitary gland becomes clinically lost in as many as 80% of brain-dead organ donors, which results in the development of DI with electrolyte imbalances, hypovolemia, and circulatory instability, and can create major problems in organ donor management .

- Other causes of polyuria, such as hyperglycemia or the use of a diuretic or osmotherapy, should be excluded before considering a diagnosis of DI .

- Usually, anterior pituitary function appears to be preserved or partially affected due to preserved pituitary blood flow .
- Most donors show normal values of thyroid-stimulating hormones (TSH), adrenocorticotropic hormones, and human growth hormones,

Systemic Inflammatory Response

- An active systemic inflammatory response is a common and typical picture of all brainstem-dead donors and can be quite severe.

- Although inflammation may be associated with trauma and other critical illnesses, it can be particularly severe in a brain-dead donor as mediators are released from the damaged brain.

- Plasma levels of interleukin-6 also increase in the donor and may lead to poorer graft utilization and subsequent graft dysfunction

Hematological Changes

- Anemia is commonly found in brain-dead patients when traumatic bleeding occurs, with coagulopathy and fluid administration further exacerbating the condition .

- Isolated head injuries are present with coagulopathy in 34% of cases . Necrotic brains release tissue thromboplastin and plasminogen activators, which are also released from cerebral injuries, and result in disseminated intravascular coagulation .

- Bleeding complications may occur due to a deranged coagulation profile (prothrombin and activated partial thromboplastin time) and thrombocytopenia .
- Leukocyte count may be elevated from the cerebral insult, with a systemic inflammatory state or nosocomial infection possibly occurring in the later stages

- an increased fibrin formation, hypofibrinolysis, as well as a higher platelet activation paired with a profound dysregulation in the von Willebrand factor production (which promotes platelet attachment to damaged vasculature), are observed .

- This prothrombotic state may contribute to formation of microthrombi in transplantable organs, and potentially to a deterioration of their function.

Hypothermia, Stress, and Metabolic Responses

- Hypothermia is a common feature in brain-dead organ donors due to the loss of thermoregulatory control, exposure to cold ambient temperatures, or massive infusions of cold intravenous (IV) fluids or blood products .

- It may also occur due to a reduced metabolic rate, excessive heat loss, or loss of protective mechanisms such as vasoconstriction or shivering .

- Preventing hypothermia is preferred rather than attempting to treat it. Once hypothermia develops may directly affect cardiac function, induce arrhythmias, coagulation cascades, and interfere with oxygen delivery to tissues

PRACTICAL ASPECTS OF ORGAN DONOR MANAGEMENT

- The target of management is to maintain physiological homeostasis in order to continue optimal organ function and to maximize graft viability in the organ recipient An early and easy-to-remember series of goals were established known as the “rule of 100” :
- systolic arterial pressure >100 mmHg
- urine output >100 ml/hr
- arterial partial pressure of oxygen (PaO2) >100 mmHg,
- HB concentration >10 mg/dL.
- Later, an additional goal was included: “blood sugar 100% normal”

Temperature Management

- Prevention of hypothermia should be preferred compared with its reversal.

- It is easier to prevent hypothermia by actively warming the donor body, and bodies with temperatures <34°C should be subjected to core warming .
- Surface warming should be performed for all patients with hypothermia and should be continued to maintain a temperature over 35.8°C before and during the retrieval operation .
- Active warming can be achieved using warm blankets, fluid warmers, and heated humidifiers in ventilator circuits , as well as by adjusting the ambient temperature

Hemodynamic goals

- Goals for the management of hemodynamic status in donors are as follows :
- (1) to maintain normovolemia;
- (2) to control blood pressure (BP);
- (3) to optimize cardiac output (CO) to maintain perfusion pressure of all organs; and
- (4) to minimize use of vasoactive agents.

- Logically, recommendations on BP values should be individualized; for example, higher BP targets for potential organ donors with known hypertension

Hypertension

- Anti-hypertensive drugs are typically not required after brain death due to the transient nature of the autonomic storm .

- Hypertension is very unlikely to occur after brain death, and as donor organs tend to be at higher risk of hypotension rather than hypertension, a conservative treatment plan is recommended .

- In the case of a hypertensive donor, the goal for mean arterial BP is <90 mmHg, but it should always be kept above 65–70 mmHg .

- If necessary, short-acting anti-hypertensive drugs, such as esmolol, sodium nitroprusside, hydralazine, labetalol, or nitroglycerine, are preferred as long-term use of anti-hypertensive drugs are usually not required

Hypotension

- Systemic hypotension is very common in brain-dead donors and may occur in up to 97% of cases.

- Signs of continuing hemorrhage (external, gastrointestinal, urinary, abdominal) should be checked, and medications that may contribute towards hypotension (anti-hypertensive drugs, β-blockers) should be avoided .

- Three management strategies are commonly adopted, and the direction of treatment depends on the clinical response. These strategies include

- volume expansion,
- vasopressors and inotropes,
- and hormonal replacement .

Table 2. Consensus recommendations [20]

Variable	Crystal City consensus	Shemie et al. (2006) [45]	ACCP/SCCM consensus [12]
Heart rate (beats/min)		60–120	
Arterial systolic pressure (mmHg)		> 100	
Mean arterial pressure (mmHg)	> 60	≥ 70	> 60
Central venous pressure (mmHg)	4–12	6–10	
Urine output (ml/kg/hr)		0.5–3	> 1
Pulse oximetry (%)		≥ 95	
Pulmonary capillary wedge pressure (mmHg)	8–12	6–10	
Cardiac index (L/min/m^2)	2.4	2.4	
Systemic vascular resistance (dyn-s/cm^5)	800–1,200	800–1,200	

Volume expansion and fluid management

- Hypovolemia is a common scenario in brain-dead donors and appropriate fluid resuscitation is usually considered the first step in correcting hypotension .

- At different centers, both crystalloids and colloids are used and often in combination .
- However, the decision for fluid selection should be considered based on serum electrolytes, sugar levels, hemodynamics of the patient, estimated volume deficiency, and polyuria from DI .

(1) Fluid

- The recommendations are as follows .

✓ (1) Crystalloids with balanced salt content should be used to avoid hypernatremia (concurrent DI). Lactated Ringer's solution and half-normal saline (0.45%) are frequently used . A solution of 0.9% normal saline may cause hyperchloremic acidosis, which increases renal vascular resistance and confounds base excess when used as a resuscitation fluid. Excessive IV fluids containing 5% dextrose may worsen hyperglycemia and hypothermia .

✓ (2) Colloids, such as hydroxyethyl starches, need to be avoided in organ donors as they can damage renal epithelial cells and cause early graft dysfunction in the transplanted kidneys .

✓ (3) Albumin solutions (4% and 20%) can be used to reduce the amount of fluid volume administered. However, it is usually only moderately effective, and the high sodium content of albumin-based solutions should also be considered .

✓ (4) Lactated Ringer's solution or half-normal saline solution (0.45%), with the addition of sodium bicarbonate at 50 mmol/L, can be given if the donor has acidosis to reduce the incidence of hypernatremia in donors

(2) Monitoring

- Hemodynamic monitoring tools are used in the assessment of volume status and responses to therapy

- Pulmonary artery or central venous catheter insertion, as well as noninvasive monitoring techniques, should be considered.
- Serial or continuous measurements of central venous pressure or pulmonary arterial obstructive pressure are necessary. Stroke volume, CO, cardiac index, and mixed venous oxygen saturation should also be monitored continuously .

Vasoactive agents

- Patients require additional vasoactive agents when adequate fluid resuscitation is not sufficient to restore BP and CO. It has been estimated that approximately 80%–90% of donors require inotropic and/or vasopressor support . There are widely divergent opinions concerning the use of vasoactive medication, with no consensus or randomized controlled trials (RCTs) to determine which drugs to use and which to avoid . Depending on local practices and protocols, noradrenaline, adrenaline, vasopressin, dopamine, and/or dobutamine are commonly used solely or in combination.

- Animal models have shown that high doses of catecholamines may cause cardiomyopathy . Although no RCTs in humans currently exist, animal models have demonstrated a reduced inflammatory response and improved oxygenation when using noradrenaline .
- Very few retrospective studies currently exist examining the selection of catecholamines for use in organ-protective intensive care.

- In Germany, norepinephrine is most often used to target parameters at low dosages, whereas in the Anglo-American arena, vasopressin is often preferred over norepinephrine. The recommended dose of noradrenaline is 0.5– 4 U/hr . In some centers, if the CO is lowered, dobutamine is also used.
- Vasopressin is highly effective in DI management and reduces the hemodynamic need for using different catecholamines . However, other studies have shown that norepinephrine increased both coronary and renal blood flow in the normal mammalian circulation , whereas vasopressin had no effect . At present, there are no convincing studies or consensus to demonstrate that one vasopressor is superior to another .
- Although dopamine is used frequently by some centers, other transplant teams prefer not to use it as dopamine causes presynaptic modulation of norepinephrine release. Therefore, prolonged dopamine infusions may cause depletion of norepinephrine stores in the heart, possibly resulting in myocardial dysfunction after transplantation . Some studies have found that combining 1-deamino-8-D-arginine vasopressin with a low dose of epinephrine may produce prolonged hemodynamic stability in brain-dead patients without causing worsening of liver or renal functions , although such approaches are still considered experimental

Combined hormonal therapy

- Although “triple-therapy” (the combination methylprednisolone, vasopressin, and triiodothyronine [T3]) remains controversial, some studies have reported that it may improve both hemodynamic stability in brain-dead patients, as well as the quality of the procured organs . Some centers use triple therapy according to their local protocol with the decision of initiating hormonal therapy undertaken in discussion with the organ retrieval teams .

- The United Network for Organ Sharing has conducted an analysis on 10 years of data covering several hormone replacement modalities and showed that the combination of a thyroid hormone, corticosteroid, insulin, and an antidiuretic hormone was the most promising in multiple organ procurement . Combined hormonal therapy is particularly indicated in patients in which volume loading and vasoactive medications have not produced hemodynamic instability .

- Hormone replacement therapy may be initiated if hemodynamic goals are not met and/or the left ventricular ejection fraction remains less than 45% . The recommended replacements are :

✓ (1) vasopressin: 1 U bolus followed by an infusion of 0.5–4.0 U/hr,

✓ (2) methylprednisolone: 15 mg/kg immediately after the diagnosis of brain death and every 24 hours afterwards. Alternatively, 250 mg followed by 100 mg/hr until organ retrieval,

✓ 3) insulin infusion to maintain blood glucose levels between 80 and 150 mg,

✓ (4) thyroxine (T4; 20 µg bolus) followed by infusions of 10 µg/hr. T3, administered as a 4 µg bolus, followed by infusion of 3 µg/hr. T4 improves hemodynamic status and prevents cardiovascular collapse in hemodynamically unstable organ donors

Anti-diuretic hormone

- If the patient develops DI, electrolytes should be monitored frequently and corrected accordingly .
- If left untreated, this may result in hypovolemia, hyperosmolality, hypernatremia, hypermagnesemia, hypokalemia, hypophosphatemia, and hypocalcemia . IV fluids should be given to replace fluid loss through urine and a balanced salt solution or fluids with low-sodium content (5% dextrose or 0.45% saline) should be used to maintain sodium levels between 135 and 145 mEq/L .
- Treatment for arginine vasopressor or antidiuretic hormone deficiency should be considered if hypotension persists despite adequate volume resuscitation and if one or more of the following criteria are identified in the absence of other causes :

✓ (1) polyuria (urine output >3–4 L/day or 2.5–3.0 ml/kg/hr),

✓ (2) normal or increased serum osmolality,

✓ (3) inappropriately diluted urine (specific gravity <1.005, urine osmolality <200 mOsm/kg H_2O),

✓ (4) hypernatremia (Na^+ >145 mmol/L).

- DI can be treated by replacement of fluid with adequate crystalloid solutions and by administration of desmopressin.

Renal Management

- As shown in experimental animal models and historical databases, kidneys are at high risk for developing ischemia because of increased levels of catecholamines at the time of brain death.
- Subsequent hypoperfusion is also possible if donor management is inadequate and is not appropriately treated .
- Effective donor management is associated with good renal graft function, even if liberal fluid therapy is avoided.
- Renal management should be achieved by appropriate fluid management and judicial use of vasopressor drugs.

- Euvolemia, even while this is an ill-defined concept, is the primary therapeutic goal, and isotonic crystalloid solutions are the preferred choice for volume replacement in the organ donor.
- In the absence of evidence of superiority of one over the other, 0.9% saline or lactated Ringer solution are both recommended .
- Starch-based synthetic colloids should be avoided because of their known adverse effects in critically ill patients generally

Table 3. Protocols for the management of brain-dead organ donors

Category	Recommendation
General management	Central line insertion and monitoring
	Arterial line insertion and monitoring
	Nasogastric tube insertion
	Foley's catheter insertion
	Care lines, intubation tube, Foley's catheter; consider changing when necessary
	Maintain the head of the bed at 30°–40° elevation
	Continue side-to-side body positioning
	Warming blankets to maintain body temperature around 36.5°C
	Maintain pneumatic compression device for preventing deep vein thrombosis
	Eye protection
	Frequent airway suctioning
	Ulcer prophylaxis
	Broad spectrum antibiotics
Monitoring	Vital signs check every 1 hour
	Urine output check every 1 hour
	Arterial blood pressure with continuous monitoring
	ABG analysis every 6 hours
	Body temperature check every 1 hour
Therapeutic target	Mean arterial pressure: >65 mmHg
	Hemoglobin: > 10 g/dl
	Sodium: < 160 mmol/L
	Potassium: 3.5–5 mmol/L
	Central venous or mixed venous oxygen saturation: >70%
	SpO_2: >92%
	Arterial blood gases within the normal range (with the exception of permissive hypercapnia)
	Lactate: <3 mmol/L
	PCO_2: 35–45 mmHg
	Blood sugar: 140–180 mg/dl
	Hourly urine output: 100–300 ml
	Central body temperature: >36.0°C

Diabetes Insipidus: Etiology

- Normally the regulation of urine production occurs in the hypothalamus, which produces arginine vasopressin (or antidiuretic hormone, ADH). After synthesis, ADH is transported to the posterior pituitary where it is stored for release.

- When these structures are infarcted after brain death, there is a rapid depletion of ADH leading to diabetes insipidus (DI) in ~60-80% of brain dead organ donors.

- DI is characterized by excessive diuresis, severe hypovolemia, and hypernatremia.
- Differential diagnosis of polyuria:

Variable	DI	Mannitol Therapy	Hyperglycemia
Serum Na (mmol/L)	> 150	> 150	> 150
Serum Osmo (mOsm)	> 300	> 300	> 300
Serum Osmolar Gap (mOsm)	Normal	> 10-15	> 10-15
Urine Output (ml/h)	> 300	> 200	> 200
Urine Na (mmol/L)	**< 10**	50-70	50-70
Urine Osmo (mOsm/L)	**< 200**	> 300	> 300
Urine Spec Gravity	**< 1.005**	> 1.020	> 1.020
Urine Glucose	Absent	Absent	Present

Diabetes Insipidus: Complications

- Hypotension due to dehydration
- • Electrolyte abnormalities secondary to free water loss:
- – Hypernatremia
- – Hypokalemia
- – Hypocalcemia
- – Hypophosphatemia
- • Severe dehydration may cause renal cellular swelling that, in turn, can cause capsular rupture of the kidneys

Diabetes Insipidus: Treatment

- Correct hypovolemia
- – 1:1 fluid replacement with D5W
- – 1:1 fluid replacement with D5 ¼ NS

- • Correct free water deficit and hypernatremia
- – Free water deficit (L) = TBW* x ([serum Na/140] – 1)
- TBW (men) = 0.6 x weight (kg)
- TBW (women) = 0.5 x weight (kg)

- • Hormone replacement therapy
- – 0.5 - 2 mcg DDAVP IV Q2h PRN

- • GOAL: hourly urine output 0.5 – 2 ml/kg

- CDI is an early sign of brain death-related endocrinopathy, and is reported in 46–86% of brain-dead organ donors . It is a consequence of failure of posterior pituitary function and depletion of ADH , and is characterized by polyuria, hyperosmolality, and hypernatremia.
- CDI should be treated with desmopressin or vasopressin depending on the patient's clinical status Desmopressin is a vasopressin analogue with greater affinity for the V2 receptor.
- It has a primary antidiuretic action and is the preferred choice for CDI in the absence of hypotension. Dosing is largely empirical.
- If further correction of hypernatremia is required once volume status is stabilized, hypotonic fluids such as 5% dextrose can be considered while being mindful to avoid hyperglycaemia.
- Vasopressin infusion is indicated when CDI occurs in association with hypotension refractory to fluid resuscitation; it acts equally at all three vasopressin receptors, so has pressor in addition to antidiuretic actions. Vasopressin use is associatedwith increased organ retrieval rates, although it is not known whether this effect is related to its reversal of hypotension, treatment of CDI, or both . Maintaining serum sodium < 155 mEq/L during the management of CDI is recommended because some studies report worse liver graft survival with higher concentrations

Table 1 Diagnostic criteria for central diabetes insipidus

Clinical feature	Diagnostic finding
Increased urine volume	Urine output > 3–4 L/day or > 2.5–3.0 mL/kg/h
Hypernatremia	Serum sodium concentration > 145 mmol/L
Normal or increased serum osmolality	Serum osmolality > 305 mmol/kg
Inappropriately dilute urine	Urine osmolality < 200 mmol/kg or specific gravity < 1.005[a]

Hyponatremia

- Hyponatremia is a common electrolyte disturbance after brain injuty. It is defined as a serum sodium concentration 135 mEq/L and is most often caused by an increased volume of the ECF due to water retention or iatrogenic causes.
- Hyponatremia is associated with several clinical manifestations, and the severity may be associated with the degree of hyponatremia. Also, rapidly occurring hyponatremia is more likely to result in symptoms than slowly developing hyponatremia.
- Seizures may occur but usually at extremely low sodium levels (115 mEq/L). Patients with brain injury may already have cerebral edema, and concomitant hyponatremia can lead to further increases in ICP and death from herniation.

- The causes of hyponatremia after brain injury are varied.

- Hyperosmotic hyponatremia is usually the result of hyperglycemia or may also occur if mannitol is given in large doses to patients with renal failure. Glucose and mannitol cause translocation of water into the ECF while reducing sodium concentration.

- Hypoosmotic hyponatremia can be categorized into 3 different etiologies, depending upon whether the ECF volume is high, normal, or low.

- Hypo-osmotic hyponatremia with hypovolemia is caused by renal sodium loss (diuretics), extrarenal sodium loss (vomiting, diarrhea, third spacing), hypokalemia, or cerebral salt-wasting syndrome (CSWs).
- Hypo-osmolar hyponatremia with normovolemia results from conditions such as hypothyroidism, glucocorticoid deficiency, or the syndrome of inappropriate antidiuretic hormone (SIADH).
- Hypo-osmolar hyponatremia with excess interstitial ECF (edema) occurs in conditions such as cirrhosis, cardiac failure, and other types of renal failure.

- *SIADH.* SIADH is one of the more common causes of hyponatremia, affecting 5%–25% of patients after brain injury. Hyponatremia results from a dilutional effect of continued ADH release despite low serum osmolality, causing increased renal conservation of water and secretion of highly concentrated urine. The specific cause of the excess secretion is unknown, but it may be due to a direct effect of damage to the hypothalamic-neurohypophyseal system or an indirect effect on this system secondary to increases in ICP. Pain and stress may also stimulate the release of ADH.
- The diagnosis of SIADH is based on first excluding other causes of hyponatremia
- Diagnosis is usually confirmed by the presence of hyponatremia, with a low serum osmolality and a high urine sodium concentration (25 mEq/L).Volume status is usually expanded or euvolemic;
- Treatment of SIADH is based upon fluid restriction. In patients with mild symptoms who are not severely hyponatremic (125 mEq/L), restriction of fluid to 800–1000 mL per day using normal saline is a reasonable option.
- Patients with severe, acute hyponatremia require more aggressive management .

- *CSWs.* The existence of CSWs has been debated for many years. For the most part, brain-injured patients with hyponatremia were diagnosed as having SIADH. Several cases of a syndrome similar to SIADH were reported whereby hyponatremic patients met criteria for SIADH but had findings of hypovolemia.

- Sivakumar et al98 examined 21hyponatremic neurosurgical patients, assessing volume status using central venous pressure and hematocrit measurements. All patients were found to demonstrate some form of hypovolemia, a scenario consistent with CSWs and not SIADH.
- A retrospective analysis of 134 subarachnoid hemorrhage (SAH) patients found that of 21 of 26 patients treated for SIADH with fluid restriction suffered cerebral infarcts. This in some way implies that these patients had CSWs rather than SIADH as fluid restriction may have predisposed already dehydrated patients to have cerebral ischemia.

Comparison of SIADH and cerebral salt wasting (CSW) syndrome

	SIADH	CSW
Serum sodium	↓	↓
Urine sodium	↑	↑
Plasma volume	↑	↓
Central venous pressure	↑ or normal	↓
PCWP	↑ or normal	↓
Hemoglobin/hematocrit	↓ or normal	↑
Serum osmolality	↓	↑ or normal
Treatment	Fluid restriction Demeclocycline Conivatptan	Hypertonic saline Fluid replacement Fludrocortisone

PCWP, pulmonary capillary wedge pressure; SIADH; syndrome of inappropriate antidiuretic hormone.

Treatment of Hyponatremia

- • D/C hypotonic fluid administration (D5W)
- • D/C administration of DDAVP/Vasopressin
- • Administer hypertonic fluids1:
- 1. Calculate sodium deficit:
- Na deficit (mEq) = TBW* x (140 – measured serum Na)
- 2. Calculate effect of treatment:
- 1L NS: Δ serum Na = (154mEq/L – measured serum Na)/(TBW* + 1)
- 1L 3% NaCl: Δ serum Na = (512mEq/L – measured serum Na)/(TBW* + 1)
- *(Note: Administer 3% NaCl @ 1-2ml/kg/hr)*
- • Administer sodium bicarbonate (NaHCO3) with coexisting acidosis (pH <7.35)
- – One amp (50mL) of NaHCO3 contains 44-54mEq Na

Hypernatremia.

- Diabetes insipidus (DI) is characterized by hypernatremia and hypotonic polyuria. DI is the result of a lack of secretion of ADH (vasopressin) or an inadequate renal response to ADH. It can be categorized as either central or nephrogenic in origin.
- Nephrogenic DI is caused by a genetic abnormality for gene expression of the vasopressin V2 receptor in the kidney or in the gene for the aquaporin-2 water channel.Hypokalemia, hypocalcemia, and drugs (lithium, cisplatin, demeclocycline) can also cause nephrogenic DI.
- Central DI is the result of damage to neurons in the hypothalamic-pituitary axis. It is common in patients with high ICP and in brain death.
- Diagnosis of DI is first based upon ruling out other potential causes of polyuria and hypernatremia. Acute renal failure, hyperglycemia, mannitol diuresis, or diuresis in response to previous fluid resuscitation can all paint such a picture. DI usually presents as an elevation of serum sodium (145 mEq/L) with polyuria (30 mL/kg/hour or 200 mL/hour), and low urine specific gravity (1.005).

- Treatment of DI involves correcting the serum sodium by providing an adequate amount of free water. Because central DI involves at least a partial deficiency of ADH, therapy to replace this hormone is also initiated. The first step involves the calculation of the patient's free water deficit.

- Hormonal therapy with vasopressin or desmopressin (DDAVP) is used to reduce both polyuria and the amount of fluid needed for free water replacement. These agents bind to V1 receptors expressed in smooth muscle, which causes vasopressor effects. Activation of V2 receptors in the collecting tubule increases water absorption along an osmotic gradient.

Treatment of Hypernatremia

- • D/C hypertonic fluid administration (3% NaCl, NS)
- • Treat DI: 1 mcg DDAVP IV Q2h PRN, .01-.04 units/min Vasopressin IV gtt
- • Administer hypotonic fluids1:
- 1. Calculate free water deficit:
- Free water deficit (in L) = TBW* x ([serum Na/140] - 1)
- 2. Evaluate volume status to determine IV fluid choice
- 3. Calculate effect of treatment:
- 1L D5W: Δ serum Na=(0mEq/L – serum Na)/(TBW*+1)
- 1L 0.45% NS: Δ serum Na=(77mEq/L – serum Na)/(TBW*+1)
- • For hypervolemic hypernatremia (caused by excessive hypertonic fluid
- administration, *not* DI), administer Lasix and D5W
- – Lasix alone will aggravate the hypernatremia because a Lasix-induced diuresis is equal to one-half isotonic saline solution

Calcium

- Calcium circulates in the blood in 3 forms:
- (1) ionized (50%);
- (2) protein-bound, primarily to albumin (40%); and
- (3) chelated to other ions (10%).
- The ionized fraction is the physiologic active calcium and calcium is under the regulation of both vitamin D and parathyroid hormone. Release of parathyroid hormone is controlled by serum concentration of calcium, magnesium, and vitamin D.
- Hypocalcemia is an extremely common electrolyte disturbance in patients with critical illness. It results from a variety of causes, including sepsis, hypomagnesemia, vitamin D deficiency, hypoparathyroidism, administration of chelating substances (citrate from red blood cell transfusions, albumin, bicarbonate), and alkalosis.

- In patients with severe brain injury , significant reductions in plasma ionized calcium have been reported. An association between hypocalcemia as an early predictor of mortality after trauma has even been suggested, there is a possible interaction between blood lactate and ionized calcium, which could be a partial explanation for the drop in calcium concentrations.

- Clinical symptoms of hypocalcemia include cardiac arrhythmias, hypotension, muscle weakness, hyperreflexia, paresthesias, agitation, confusion, and seizures.

- Hypercalcemia is uncommon in brain injury patients but may be associated with prolonged mobilization. Hypercalcemia is associated with a reduced neuromuscular excitability. Increasing renal calcium excretion with IV hydration and diuretics may treat hypercalcemia associated with reduced mobilization. Accumulation of central nervous system calcium has been recognized as an important pathway to secondary neuronal death. Excess calcium can be both directly and indirectly toxic by initiating many processes of the secondary neuronal injury cascade. Calcium is extremely important for maintaining membrane potentials and in promoting release of neurotransmitters. Therefore, under normal conditions, calcium is tightly regulated. During conditions of cerebral ischemia, depolarization and alterations in ion channel permeability resulting in an excess of intracellular calcium occur. The major mechanisms for cell death from increased intracellular calcium include activation of calciumdependent enzymes and accumulation of calcium in the mitochondria (Figure 1).The cysteine protease calpain is activated by high intracellular calcium concentrations and results in subsequent irreversible changes to the cell membrane and cytoskeleton, which affects the membrane permeability. The other important mechanism for neuronal injury is binding of calcium to mitochondrial membranes, leading to depolarization with a reducution in ATP and generation of reactive oxygen species
- Calcium-mediated damage to the mitochondria may also release proapoptotic facto resulting in delayed neuronal death

- There also seems to be a complex interaction between calcium and apoptosis. Studies have suggested that increasing intracellularcalcium will trigger neuronal apoptosis, whereas other studies have suggested apoptosis may be associated with lower intracellular calcium. It has been theorized that both calcium- overload and calcium-starved states may occur after cerebral ischemia, but may happen at different times in different neurons. The role of calcium in neuronal death after TBI as described above leads to several trials evaluating the role of calcium channel antagonists as potential neuroprotective therapy. The results of these trials only showed modest improvement in a subgroup of TBI patients with traumatic subarachnoid hemorrhage. Although nimodipine treatment has become a standard of care after aneurysmal subarachnoid hemorrhage according to improvement in neurologic morbidity, it does not seem to have a role after TBI. Experimental evidence suggests that exogenous administration of these agents significantly attenuates neuromotor and cognitive dysfunction after TBI. The effects of calcium within the central nervous system after neurologic injury are complex and are under considerable debate. The mechanisms associated with calcium-mediated toxicity have been extensively investigated and identified. Future pharmacologic interventions may target intracellular calcium homeostasis instead of the past endeavors of targeting absolute calcium concentrations.

Magnesium

- Magnesium is an important cation that has been known to be involved in the functioning of over 300 enzymes that regulate energy transformation, lipid and nucleic acid metabolism, and protein synthesis.
- Magnesium is predominantly an intracellular electrolyte, with less then 2% located within the extracellular fluid compartment.
- Nonetheless, extracellular magnesium is important for synaptic transmission in the peripheral and central nervous system. Cerebrospinal fluid (CSF) and brain magnesium (1–1.35 mg/dL) are regulated by the cerebrovascular endothelium and choroid plexus and remain somewhat stable within the brain, even during serum magnesium deficiency..

- *Most Common* Etiology:
- • Hypokalemia often causes concurrent low magnesium secondary to accelerated
- renal loss or poor Na/K pump function
- • Massive transfusion of blood products preserved with citrate.
- • Other: trauma, burns, surgery, sepsis, GI loss, renal loss, malnutrition, alcoholism
- *Most Common* Clinical Manifestations:
- • EKG changes: prolonged QT and PR interval, widening QRS complex
- • Arrhythmias: ventricular arrhythmias, torsades de pointes

Treatment of Hypomagnesemia

- Replacement therapy
- – Magnesium Sulfate (infuse @ 1-2g/hr)

Mg^{2+} level	Replacement Dosing
1.6 – 1.9 mg/dL	2 g Mag Sulfate IVPB over 1 hr
< 1.6 mg/dL	4 g Mag Sulfate IVPB over 2 hrs

Other Electrolytes

- Other common electrolyte disturbances in brain injury patients include hypokalemia and hypophosphatemia. These deficiencies commonly occur due to decreased dietary intake or increased renal loss, especially in patients who receive diuretic therapy. Renal excretion is also increased in association with catabolic losses from the trauma or from excess fluid administration. Hypokalemia appears to be common in TBI patients due to increased adrenergic stimulation and subsequent intracellular shift of potassium.

- Hypokalemia may also be the result of hypomagnesemia due to magnesium's role in activating the sodium/potassium pump. Magnesium deficiency means impaired effectiveness of the sodium/potassium pump, whereby insufficient potassium can be pumped into the cell, although the potassium supplymay be great enough. Therefore, correction of hypomagnesemia is imperative for correction of low serum potassium concentrations. Clinical manifestations of hypokalemia are generally cardiac in nature but may also be manifested as hyporeflexia and generalized weakness. Diligent monitoring of serum potassium levels with IV replacement is necessary for patients in the intensive care unit. Replacement is generally required when the potassium is 3.5 mEq/L.

- Hypophosphatemia also occurs as a result of increased renal loss but is also reported in association with respiratory alkalosis from prolonged hyperventilation causing intracellular shifts of phosphate.34 Clinical signs of hypophosphatemia do not usually appear until serum phosphate concentration is below 1.0 mg/dL and is manifested as altered mental status, muscle weakness, seizures, respiratory insufficiency, and ventricular dysfunction.


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