Acid – Base Disorders

- Acid – base disorders are very common in the NCCU
- The normal pH range is 7.35–7.45; alkalosis is defined as pH >7.45, and acidosis is defined as pH <7.35
- pH is a measure of the hydrogen ion concentration in the extracellular fluids and is determined by the pCO₂ and HCO₃ concentration
  - \([H^+] \text{ (meq/L)} = 24 \times (\text{PCO}_2/\text{HCO}_3)\)
- The initial change in PCO₂ or HCO₃ is called the primary disorder; the subsequent change is called the compensatory or secondary disorder
- Compensatory changes frequently will not return the pH to the normal range but will serve to limit the effect of the primary derangement
- Acid – base disorders are of particular concern in neurophysiology because of their effects on cerebral blood flow (CBF)
- Acidosis (decrease in pH) results in cerebral vasodilation, whereas alkalosis (increase in pH) results in cerebral vasoconstriction
  - As pH increases, cerebral vasoconstriction also increases, resulting in decreased CBF and therefore decreased cerebral blood volume and ICP
- Changes in acid – base status within the blood are transmitted across the blood–brain barrier (BBB) via CO₂ rather than by H⁺ ions; the BBB is impermeable to H⁺, but CO₂ crosses freely
- The subsequent change in the CSF pH is a result of the conversion of CO₂ + H₂O to H⁺ and HCO₃ by carbonic anhydrase
The pH of the CSF returns to normal after 6–8 h, as HCO$_3^-$ is either retained or extruded across the BBB despite ongoing hyper- or hypocapnia, respectively.

As the CSF pH returns to normal, CBF also trends toward normal.

**Primary Acid: Base Disorders**

- **Respiratory acidosis** – increased PaCO$_2$
  - Compensation – subsequent increase in HCO$_3^-$
  - Neurologic consequence
    - CBF increases 1–2 mL/100 g/min for each 1 mmHg change in PaCO$_2$ within the PaCO$_2$ range of 20–80 mmHg
    - Hypoventilation and hypercapnia can exacerbate an already elevated intracranial pressure in a patient with cerebral edema
  - Etiology
    - Hypoventilation
    - Increased CO$_2$ production from hypermetabolic state such as hyperthermia, fever, or seizures
    - Decreased cardiac output, resulting in accumulation of CO$_2$ in blood and tissues

- **Respiratory alkalosis** – decreased PCO$_2$
  - Compensation – subsequent decrease in HCO$_3^-$
  - Neurologic consequence
    - CBF decreases 1–2 mL/100 gm/min for each 1 mmHg change in PaCO$_2$ within the PaCO$_2$ range of 20–80 mmHg
    - Decreased CBF due to hypocapnia/hyperventilation can be detrimental to brain tissue that is already suffering from ischemia
  - Hyperventilation can be a useful method for temporarily decreasing CBF and ICP in patients at risk for impending herniation
  - Etiology
    - Hyperventilation

- **Metabolic acidosis** – decreased HCO$_3^-$
  - Compensation – subsequent decrease in PaCO$_2$ (hyperventilation)
  - Neurologic consequence
    - Primarily a result of the compensatory change in PaCO$_2$
    - Hypoxia (PaO$_2$ <60 mmHg) rapidly increases CBF most likely due to cerebral vasodilation induced by lactic acid
  - Differential includes anion gap vs. non-anion gap
Anion gap = Na – (Cl\(^{-}\) + HCO\(_3\)) = 12 (±4)
- Most of the normal anion excess is due to albumin

An elevated anion gap is due to the addition of fixed anions
- Lactic acid, ketoacidosis, end-stage renal failure, methanol, ethanol, salicylate toxicity

A normal anion gap acidosis is due to a net gain in chloride ions
- Diarrhea, early renal insufficiency, resuscitation with isotonic or hypertonic saline, renal tubular acidosis, acetazolamide

Metabolic alkalosis – increased HCO\(_3\)
- Compensation – subsequent increase in PCO\(_2\) (hypoventilation)
- Neurologic consequence
  - Again, this is primarily due to the compensatory change in PaCO\(_2\), resulting in increased CBF
- Etiology
  - Administration of NaHCO\(_3\)
  - Contraction alkalosis from overdiuresis (kidney retains HCO\(_3\) ions to maintain electrical neutrality while losing Cl\(^{-}\) ions)
  - Any time the loss of chloride ions exceeds the loss of sodium ions (nasogastric suctioning)

Electrolyte Disorders

- Electrolyte disorders are common and important in any critically ill patient and are of particular concern in patients with CNS disturbances
- They may occur as a part of the disease process, or they may be iatrogenic
- If unrecognized or persistently severe, the consequences of electrolyte derangement may become life threatening

Sodium
- Sodium cannot move freely across cell membranes and is the primary determinant of tonicity or effective osmolarity
- Isomotic solutions have the same number of dissolved particles, regardless of the amount of water that would flow across a given membrane barrier
  - In contrast, solutions are isotonic when they would not cause water to move across a membrane barrier, regardless of the number of particles dissolved
  - Example – 150 mM NaCL added to plasma is approximately isosmotic & isotonic to brain, and little water is therefore passed between plasma and brain.
150 mM alcohol in water, however, is isosmotic but hardly isotonic (it is quite hypotonic), as it readily passes into brain, with water also following, thus promoting edema.

Tonicity is the primary determinant of total body water as well as the distribution of body water between the intracellular and extracellular compartments.

- Hypernatremia and hyponatremia are disorders of water balance rather than disorders of sodium balance because it is the movement of water between the intra- and extracellular compartments that results in the change in serum sodium concentration.
- For any given serum sodium concentration (hypo-, eu-, hypernatremia), the actual amount of total body sodium may be low, normal, or high, which means that each state can actually be a hypo-, iso-, or hypertonic state, respectively.

During normal homeostasis, total body water is tightly coupled to total body sodium; for example, an excess of total body sodium (eating a really salty meal) results in the kidneys retaining more free water, and thus eunatremia is maintained; however, in some disease states, the body’s compensatory mechanisms become disturbed and unable to fully compensate for sodium and water losses or gains.

- These states result in an uncoupling of total body water and sodium such that volume status must be assessed by physical exam independently of total body sodium and sodium concentration.
- Some states are very common; others are very unlikely to occur, while others are iatrogenic.

**Hyponatremia**

- Defined as serum sodium <135 meq/L
- Hyponatremia always represents an excess of free water relative to sodium.
- Hyponatremia in the neurocritical care patient most frequently occurs due to inappropriate water retention or inappropriate sodium + water loss.

- Normal sodium stores – gain of free water with only minimal changes in sodium.
  - Hyperglycemia – non-sodium osmoles (glucose) in the extracellular fluid draw water from the intracellular space, creating hyponatremia; each 100 mg/dL glucose over 100 results in an approximate 1.6 meq/L decrease in serum sodium, representing a hypertonic state.
  - Azotemia – excess urea can result in an increase in total body water, leading to hyponatremia; however, as urea moves freely across cellular membranes this is actually an isotonic state.
  - Psychogenic polydipsia
  - Syndrome of inappropriate antidiuretic hormone secretion (SIADH)
ADH is normally secreted when an increase in plasma osmolarity is detected by the hypothalamus or a decrease in plasma volume is detected by the peripheral and central baroreceptors.

ADH secretion is considered inappropriate when the above criteria are not present or when it is secreted in the setting of low serum osmolarity.

Findings include:

- Urine is inappropriately concentrated (>100 mOsm/kg H$_2$O)
- Urine volume will be normal or low
- Plasma is hypotonic (<280 mOsm/kg H$_2$O)
- Patients demonstrate normal sodium handling by the kidneys, and urine sodium excretion remains >20 meq/L
- Extracellular fluid volume remains normal or slightly elevated

Etiology:

- Exact etiology is unclear
- SIADH may be associated with brain tumors, subarachnoid hemorrhage (SAH), traumatic brain injury, stroke, meningitis or encephalitis, or may be drug induced (e.g., carbamazepine)

Other reasons for excessive ADH secretion must be ruled out; e.g., hypothyroidism, mineralocorticoid insufficiency, hypotension, hypovolemia, positive-pressure ventilation, pain, stress, or lung malignancy.

- Low sodium stores – loss of sodium is greater than loss of water
  - Diuretic overuse or diarrhea/vomiting followed by volume replacement with free water
  - Adrenal insufficiency – decreased ACTH (adrenocorticotropic hormone) secretion or primary insufficiency (Addison disease), resulting in insufficient release of mineralocorticoid (aldosterone)
  - Cerebral salt wasting (CSW) – a special form

- Characterized by excessive sodium loss accompanied by excess water loss; most likely due to impaired sodium reabsorption in the proximal renal tubule
  - Theories are plentiful, but the impaired sodium reabsorption may be due to decreased sympathetic input to the kidneys or due to the release of natriuretic peptides, such as brain natriuretic peptide, by injured brain

- Laboratory evaluation is similar to that for SIADH, with exception of extracellular fluid volume
  - Urine volume will be normal or high
  - Plasma is hypotonic (<280 mOsm/kg H$_2$O)
  - Urine sodium excretion remains >20 meq/L
  - Extracellular fluid volume becomes increasingly depleted
Primary distinguishing features between CSW and SIADH are presence of hypovolemia and a negative sodium and fluid balance.

CSW shares many of the same associated disease states as SIADH; recent evidence suggests that many conditions previously thought to be associated with SIADH such as meningitis, SAH, TBI, and pituitary surgery are more likely to be associated with CSW due to the presence of hypovolemia.

Restoration of a positive sodium balance requires the infusion of hypertonic saline and may require the use of fludrocortisone, a synthetic mineralocorticoid.

SAH

- Hyponatremia is the most common and severe electrolyte abnormality after SAH.
- Hypovolemia and hyponatremia are likely due to CSW and occur 2–10 days after aneurysm rupture; they are frequently associated with cerebral vasospasm and are particularly concerning, as they further increase the risk of delayed cerebral ischemia.

- High sodium stores – excess of sodium and water, with the water gain exceeding the sodium gain

  ▲ Cardiac, renal, or hepatic failure

Neurologic manifestations

- Symptoms usually do not develop until serum sodium drops to <120 meq/dL; however, a rapid decrease in serum sodium concentration is more likely to be symptomatic than chronic hyponatremia.
- Symptoms include headache, anorexia, nausea, vomiting, malaise, confusion, or lethargy.
- If untreated, symptoms may progress to metabolic encephalopathy associated with cerebral edema, elevated ICP, and tonic-clonic seizures.
- As extracellular hypotonicity develops, water shifts intracellularly to reestablish equilibrium (cellular edema).

  ▲ During gradual development of hyponatremia, the brain compensates by extruding intracellular inorganic solutes; this is followed by water loss as the brain becomes hypotonic relative to its environment, helping to reduce the degree of cerebral edema.

Treatment

- Volume status should be assessed first.
- Patients with hypovolemia require immediate replacement with isotonic saline to maintain hemodynamic stability and restore intravascular volume.
- The sodium deficit may then be calculated to guide further therapy.

  ▲ $Na^+ \text{ deficit (meq)} = \text{Normal TBW} \times (130 - \text{Current } Na^+)$
• In patients with isovolemia or hypervolemia, infusion of furosemide with isotonic fluids may be helpful
• Euvolemic patients with asymptomatic hyponatremia may be treated with free water restriction alone or in combination with oral sodium supplementation
• Severely symptomatic patients may require the use of hypertonic saline
• Fludrocortisone
  ▲ A synthetic mineralocorticoid
  ▲ May be used for mineralocorticoid replacement in patients with primary adrenal insufficiency
  ▲ May be considered in refractory CSW with ongoing losses of sodium and free water (0.1–0.2 mg daily)
• Important risk – osmotic demyelination syndrome
  ▲ Results from a too-rapid correction of serum sodium that triggers demyelination of susceptible neurons, particularly the pons
  ▲ Symptoms progress over hours to days and include spastic paralysis, pseudobulbar palsy, and decreased level of consciousness
  ▲ Correction of serum sodium should be limited to 0.5 meq/L/h and no more than 8–10 mmol/L over 24 h to limit risk
♦ Hypernatremia
• Defined as a serum sodium >145 meq/L
• Hypernatremia always represents a deficiency in water relative to total body sodium
  ▲ Normal sodium stores – loss of free water with minimal or no loss of sodium
□ Diabetes insipidus (DI)
  ◦ Most frequently occurs after pituitary or diencephalic surgery
  ◦ May occur with brain neoplasms, anoxic brain injury, meningitis, or cerebral edema
  ◦ Injury to the hypothalamus results in insufficient secretion of ADH, rendering the kidneys unable to concentrate urine in the face of a rising serum osmolarity
  ◦ Diagnosis
    — High urine output
    — Serum Osm >290 mOsm/kg
    — Urine specific gravity <1.010
  ◦ Associated with loss of other electrolytes due to high urine output
  ◦ Is often temporary, lasting 3–5 days
  ◦ Treatment includes vasopressin (DDAVP); sodium and serum osmolarity should be checked frequently, as the use of vasopressin in the setting of resolving DI may result in hypervolemia and hyponatremia
DI may be nephrogenic or neurogenic; however, nephrogenic DI rarely occurs in the neuro ICU

▲ Low sodium stores – loss of water greater than the loss sodium (loss of hypotonic fluid)

☐ Excessive sweating, vomiting, or diarrhea without volume replacement
☐ Iatrogenic

○ Mannitol is frequently used in the NCCU for treatment of acutely elevated ICP and results in free water loss greater than sodium loss; serum osmolality and sodium should be monitored

▲ High sodium stores – gain of more sodium than water (gain of hypertonic fluid)

☐ Frequently iatrogenic in the NCCU; hypertonic saline is used for treatment of cerebral edema due to stroke or TBI as well as to replace sodium losses during CSW
☐ To avoid development of symptoms, an upper limit to treatment must be set and the sodium levels must be frequently checked to ensure that levels are not rising too rapidly

♦ Neurologic manifestations

• Symptoms usually do not develop until Na >160 mmol/L, but a rapid increase in sodium concentration may cause symptoms at lower levels
• Symptoms primarily include a decreased level of consciousness and confusion that may progress to tonic-clonic seizures
• Intracellular fluid in the brain becomes hypotonic relative to the extracellular fluid during hyponatremia; water then shifts out of the cells along the osmotic gradient, resulting in a reduction of intracellular volume and symptoms (cellular contraction)

▲ This mechanism is frequently used to advantage in the NCCU for the treatment of cerebral edema and elevated ICP; hypertonic saline infusion creates an osmotic gradient to draw water out of brain cells

• The brain is able to compensate for acute hypernatremia over a matter of hours by accumulating electrolytes intracellularly; cerebral osmolality and brain volume are then restored
• Chronic hypernatremia results in brain accumulation of organic osmolytes over several days (myoinositol, β taurine, small-chain amino acids); restoration of cerebral osmolality results in restoration of brain volume

▲ The brain is unable to rapidly eliminate the organic osmolytes; rapid correction of hypernatremia or rapid discontinuation of hypertonic saline therapy can therefore result in rebound cerebral edema as the osmolytes and the accumulated electrolytes continue to draw water into brain cells
Electrolyte and Metabolic Derangements

Treatment

- Volume status should be assessed, and hypovolemia should be treated with isotonic fluids to maintain hemodynamic stability
- Free water deficit is then calculated using the following formula:
  \[ \text{TBW} = \text{total body water} \]
  \[ \text{TBW deficit} = \text{Normal TBW} - \text{Current TBW} \]
  \[ \text{Current TBW} = \text{Normal TBW} \times \left(\text{Normal P}_{Na}/\text{Current P}_{Na}\right) \]
  \[ \text{Replacement Volume} = \text{TBW deficit} \times \left(1/1 - X\right) \]
  \[ X = \text{concentration of sodium in the replacement fluid} \]
- As described above, acute hypernatremia may be corrected over a few hours as the brain is able to rapidly eliminate accumulated electrolytes
- To avoid the risk of cerebral edema, chronic hypernatremia should be corrected at a rate not greater than 0.5 meq/L/h and no more than 10 meq/L/day, as the brain requires days to eliminate accumulated organic osmoles

Potassium

- Potassium is the major intracellular cation
- Only 2% of potassium stores are found extracellularly, and only 0.4% is found in plasma; therefore, serum potassium is a poor measure of total body potassium
- Total body potassium is \( \sim 50 \text{ meq/kg} \)
- Large intracellular stores of potassium are very effective at replenishing extracellular potassium losses; as a result, the relationship between the changes in total body potassium and serum potassium is curvilinear such that serum potassium changes occur twice as rapidly when potassium stores are in excess than they do when potassium stores are depleted

Hypokalemia

- Defined as serum K < 3.5 meq/L
- Etiology
  - Transmembrane shift
    - Catecholamines (i.e., \( \beta \) agonists) stimulate Na\(^+\)/K\(^+\) ATPase activity
    - Alkalosis – hydrogen ions are shifted extracellularly in exchange for potassium ions
    - Hypothermia
    - Insulin enhances Na/K ATPase activity
    - Hypertonicity – the increase in electrochemical gradient favors the movement of ions out of cells
- Potassium depletion
  - Renal losses
Diuretic therapy increases the distal tubular flow and sodium delivery to the distal tubule, stimulating the secretion of potassium via Na⁺/K⁺ ATPase.

Mannitol is a frequently used diuretic to treat elevated ICP in the NCCU; because of its potassium wasting properties, serum K⁺ should be monitored and replaced as needed.

Mineralocorticoids

- Aldosterone stimulates the reabsorption of sodium and the secretion of potassium in the distal tubule.
- Fludrocortisone therapy is often employed in the NCCU in the treatment of hyponatremia in the context of CSW; serum potassium levels should be monitored and replaced to avoid associated hypokalemia.

ADH stimulates potassium secretion at the distal tubule independent from its water-retaining effects.

Magnesium depletion

- Impairs potassium reabsorption across the renal tubules.

High-dose steroids used to treat spinal cord injury and mineralocorticoid therapy for CSW both potentiate renal losses of potassium.

- Extrarenal losses
- Diarrhea

Clinical relevance

- Initially often asymptomatic but important due to its role in cardiac conduction.
- Hypokalemia can be associated with nonspecific EKG changes, including U waves, flattening or inversion of T waves, and prolongation of the QT interval.
- Hypokalemia promotes cardiac dysrhythmia when combined with other pro-dysrhythmic conditions such as ischemia, digitalis toxicity, or magnesium depletion.

SAH is frequently associated with EKG changes and sinus dysrhythmia; EKG changes generally disappear within 24 h and are considered a marker for the severity of the SAH rather than a predictor of potential cardiac complications or clinical outcome; nonetheless, one should be wary of hypokalemia in the setting of SAH-induced EKG changes, as the combination may potentiate a cardiac dysrhythmia.

Stroke patients frequently have coexisting cardiac disease; for example, the case of an embolic stroke due to atrial fibrillation with a patient who not only has coexisting cardiac disease but also receives digoxin for adequate heart rate control.
- **Hyperkalemia**
  
  ◆ Defined as serum $K^+ > 5.5$ meq/L
  ◆ Transmembraneous shift
    
    - β antagonists/digitalis
    - Acidosis
    - Rhabdomyolysis
      
      ▲ Occasionally, patients with neurologic disease are found after being unconscious for an unknown period of time; a high level of suspicion for rhabdomyolysis is indicated in these patients, and serial creatinine kinase and potassium level checks are indicated.

  ◆ Impaired renal excretion
    
    - Renal insufficiency, renal failure
    - Adrenal insufficiency
    - Drugs
      
      ▲ ACE inhibitors/adrenergic receptor binders
      ▲ $K^+$-sparing diuretics
      ▲ NSAIDs
      ▲ Heparin – e.g., patients with ischemic stroke may be placed on a heparin infusion
      ▲ Antibiotics – trimethoprim-sulfamethoxazole, potassium penicillin
    
    - Blood transfusion
      
      ▲ Potassium leaks from erythrocytes in stored blood
      ▲ The extra potassium is normally cleared by the kidneys, but in circulatory shock that requires transfusion greater than one blood volume, potassium can accumulate and result in hyperkalemia

  ◆ Clinical relevance
    
    - Slowing of electrical conduction within the heart can begin at levels of 6.0 meq/L and is almost always present by 8.0 meq/L; progressive EKG changes occur
      
      ▲ Peaked T waves $\rightarrow$ flattened P waves $\rightarrow$ lengthened PR interval $\rightarrow$ loss of P waves with prolonged QRS $\rightarrow$ ventricular fibrillation $\rightarrow$ asystole
    
    - Hyperkalemia is a relatively uncommon electrolyte abnormality in NCCU patients; however, it can occur, particularly in those who have coexisting renal failure

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**Magnesium**

- Second-most abundant intracellular cation after potassium
- Only 1% of magnesium is located in the plasma; therefore, total body stores of magnesium can be low despite normal serum magnesium levels
Magnesium acts as a cofactor for many enzymatic reactions involving ATP

- Regulates the movement of calcium into smooth muscle cells, rendering it important for cardiac contractility and vascular tone
- Regulates calcium influx into neuronal cells via glutamate receptor – associated ion channels; magnesium partially blocks the receptor and reduces calcium currents, thereby limiting calcium overload of neurons in ischemia/reperfusion; magnesium has been suggested to have neuroprotective properties

Hypomagnesemia

- Defined as serum Mg < 1.3 meq/L
- Etiology
  - Diuretic therapy – loop diuretics > thiazide diuretics
    - Urine magnesium losses parallel urine sodium losses
    - Does not occur with potassium-sparing diuretics
  - CSW
    - Magnesium follows sodium in the renal tubules; therefore, large sodium losses in CSW also result in significant magnesium losses
- Clinical relevance
  - Symptoms include exacerbation of neurologic dysfunction, apathy, delirium, muscle weakness, hyperreflexia, muscle spasms, ataxia, nystagmus, and seizures
  - Associated electrolyte abnormalities
    - Hypokalemia and hypocalcaemia can be refractory to replacement therapy in the setting of hypomagnesemia
    - Low magnesium impairs the release of parathyroid hormone and end-organ responsiveness to parathyroid hormone
  - Magnesium depletion results in prolonged cardiac cell repolarization and prolonged Qt intervals on EKG
    - Torsade de pointes – a form of ventricular fibrillation most frequently associated with hypomagnesemia; the primary treatment is magnesium infusion
  - Neuroprotective agent
    - Magnesium may act as a neuroprotective agent in brain ischemia via several mechanisms
      - Acts as an endogenous calcium-channel antagonist
      - Inhibition of release of excitatory neurotransmitters such as glutamate
Electrolyte and Metabolic Derangements

- NMDA-receptor antagonism
- Direct vascular smooth muscle relaxation

- Currently, the use of hyperacute magnesium therapy to provide neuroprotection after stroke is under investigation

- SAH
  - ~30% of patients who present with SAH have coexisting hypomagnesemia upon admission
  - Relationship between low magnesium levels, SAH, and myocardial stunning remains unclear
  - Combination of low magnesium with stunned myocardium represents a pro-dysrhythmic state, and magnesium should be replaced in these patients

- Prevention of seizures – low magnesium levels reduce the seizure threshold, and magnesium is the primary agent used to prevent seizures during preeclampsia in pregnancy

- Hypermagnesemia
  - Defined as a serum Mg >2.0 meq/L
  - Etiology
    - Renal failure
    - Iatrogenic – magnesium infusion for neuroprotection or in the context of preeclampsia
    - Hemolysis
    - Adrenal Insufficiency
    - Lithium intoxication
    - Hyperparathyroidism
  - Clinical relevance
    - Hypermagnesemia becomes symptomatic at levels >4 meq/L
    - Progress of symptoms – hyporeflexia → first degree AV Block → complete heart block → respiratory failure → cardiac arrest
    - Not a common problem in the NCCU but should be on the differential of patients with hyporeflexia

Calcium

- Primarily an extracellular cation that exists in protein-bound (inactive), anion-bound (inactive), and ionized (active) forms
- Tightly regulated by parathyroid hormone (PTH) and vitamin D; PTH secretion by the parathyroid gland results in increased reabsorption of calcium in the thick ascending limb and the distal tubule of the nephron
Calcium is the primary mediator of muscle contraction

Calcium is of primary importance in the neurocritical care environment due to its central role in neuronal death after CNS injury

- Cytotoxic intracellular calcium movement is mediated via glutamate receptors, voltage-gated calcium channels, and pH-dependent calcium channels
- Influx of calcium from the extracellular space and the endoplasmic reticulum results in the activation of cellular injury and death cascades

Calcium-channel blockers

- The calcium-channel antagonist nimodipine has been shown to reduce the incidence of cerebral ischemia due to vasospasm following SAH and should be initiated as soon as possible following hemorrhage and continued for 21 days; a similar benefit has not been seen in stroke patients

Hypocalcemia

- Defined as serum ionized Ca <1.1 mmol/L
- Rather uncommon in the NCCU patient population
- Relevant causes include phenytoin, phenobarbital, hypoparathyroidism after neck surgery, renal failure, and blood transfusion (citrate anticoagulant in packed red blood cells binds calcium)
- Respiratory alkalosis as a result of hyperventilation (i.e., for treatment of elevated intracranial pressure) results in an increase in protein binding of calcium
- Clinical manifestations are related to cardiac and neuromuscular conduction and to depressed myocardial contractility
  - Cardiac findings include prolonged QT and ST intervals, decreased cardiac output, hypotension, and bradycardia, and can progress to ventricular dysrhythmias
  - Neuromuscular symptoms include tetany, parathesias, weakness, and seizures

Hypercalcemia

- Defined as serum ionized Ca >1.3 mmol/L
- Also relatively uncommon in the NCCU patients
- Relevant causes include malignancies, renal failure, prolonged immobilization, phosphorus depletion, hyperparathyroidism, lithium, and thiazide diuretics
- Clinical manifestations involve the gastrointestinal, cardiovascular, renal, and neurologic systems
  - Cardiovascular – increased vascular resistance, QT shortening, occasional dysrhythmias
  - Neurologic – confusion, lethargy, memory impairment, weakness, hypotonia, and hyporeflexia leading to progressive obtundation and coma
**Phosphate**

- The most abundant intracellular anion; phosphate is important for membrane structure, cellular energy, the production of ATP, cell transport, and intracellular signaling cascades.
- Depletion of high-energy intracellular phosphates is considered crucial for the development of a delayed cerebral deficit in the context of cerebral vasospasm, as well as following acute cerebral ischemia.
- Hypophosphatemia

  - Defined as serum Phos <2.5 mg/dL or 0.8 mmol/L
  - Etiology
    - TBI
    - Malnutrition
    - Hypomagnesemia or hypocalcemia
    - Phosphorus-binding antacids – sucralfate, aluminum salts
    - Drugs – diuretics, steroids, β agonists
  - Clinical relevance
    - Phosphate is a major component in the production of cellular energy (ATP); therefore, phosphate depletion is concerning but can be compensated for some time; hypophosphatemia is generally asymptomatic until severe; symptoms are generally manifested as impairment in production of cellular energy
      - ▲ Cardiac failure
      - ▲ Hemolytic anemia (decreased erythrocyte deformability)
      - ▲ Depletion of 2,3-DPG, resulting in tissue hypoxia
      - ▲ Muscle weakness, including respiratory insufficiency
      - ▲ Neurologic symptoms – ataxia, tremor, irritability, and seizures
      - ▲ Impaired enzyme function
      - ▲ Immune system
  - Refeeding syndrome
    - ▲ Can occur in any nutritionally depleted patient but is particularly common among chronic alcoholics
    - ▲ Hypophosphatemia can be profound and occurs as tissues begin to rebuild themselves upon the initiation of nutritional support
      - □ May lead to muscle weakness, including respiratory muscle weakness, and glucose intolerance
      - □ May be associated with other electrolyte abnormalities (hypocalcemia, hypokalemia, or hypomagnesemia), further exacerbating muscle weakness
Hyperphosphatemia
- Defined as serum Phos >4.5 mg/dL or 1.45 mmol/L
- Etiology
  - Renal insufficiency
  - Cellular necrosis – rhabdomyolysis, sepsis, multiple trauma, tumor lysis
- Rapid increases in serum phosphate can lead to development of severe hypocalcemia; symptoms are related to the hypocalcemia

Metabolic Disorders and Endocrinopathies
- Metabolic disorders are more common in the medical ICU and may be the reason for admission; they remain important in the NCCU for two primary reasons
- Metabolic disorders and endocrinopathies should always remain in the differential diagnosis of encephalopathy
- Metabolic disorders may occur as comorbidities in any patient, including neurosurgical or neurologic patients
- Hyperglycemia
  - Hyperglycemia (defined as blood glucose >150 mg/dL) in the setting of ischemic brain injury has been shown to be an independent predictor of poor outcome
  - In animal studies, hyperglycemia before or during ischemic injury has been shown to increase severity of injury
  - Elevation of blood glucose in the setting of severe ischemia or TBI is most likely due to the physiologic stress caused by the injury
  - The exact blood glucose level at which insulin therapy should be initiated remains undefined; however, most practitioners aim to keep blood sugar levels <150 mg/dL and >80 mg/dL in critically ill patients with CNS disease
  - Two specific conditions that may result in severe hyperglycemia and may be the reason for admission to the ICU are nonketotic hypersmolar coma (NKHC) and diabetic ketoacidosis
    - NKHC
      ▶ A form of hypertonic encephalopathy similar to that of hypernatremia
      ▶ Patients usually have enough endogenous insulin to prevent ketosis
      ▶ Patient may or may not have a prior history of diabetes, but onset is usually precipitated by physiologic stress
      ▶ Encephalopathy usually presents as altered mental status but may progress to focal deficits and seizures
      ▶ Findings
        - Blood glucose usually >1,000 mg/dL
        - Persistent osmotic diuresis leads to profound hypovolemia
      ▶ Treatment
        - Volume resuscitation with isotonic fluids or colloids
Replacement of free water once intravascular volume has been restored; pseudohyponatremia is likely to be present, and resuscitation of hypovolemic state requires high degrees of NaCl, as the serum glucose level decreases with treatment.

Restoration of brain cell volume may occur rapidly; therefore, volume replacement should occur slowly.

Insulin therapy can be initiated after volume status has been restored.

- Insulin therapy via infusion: start at 0.1 unit/kg bolus + 0.1 unit/kg/h with goal of decreasing blood glucose by 50–70 mg/dL/h; decrease infusion of insulin to 0.05 units/kg/h when a serum glucose of 200 mg/dL has been reached.

**Diabetic ketoacidosis**

- Usually seen in Type I (insulin-dependent) diabetics but may be the presenting sign of new-onset diabetes.
- May be seen in a previously well-controlled diabetic who is experiencing acute physiologic stress such as infection or sepsis.

**Findings**

- Blood glucose usually > 250 mg/dL but <800 mg/dL
- Serum bicarbonate <20 meq/L
- Elevated anion gap
- Ketones in blood and urine

**Treatment**

- Volume resuscitation with isotonic fluids; fluid deficit is usually 100 mL/kg
- Insulin therapy via infusion: start at 0.1 unit/kg bolus + 0.1 unit/kg/h with goal of decreasing blood glucose by 50–70 mg/dL/h; decrease infusion of insulin to 0.05 units/kg/h when serum glucose of 200 mg/dL has been reached
- Replace potassium; correction of underlying acidosis in combination with insulin therapy will drive potassium intracellularly; as patients are generally potassium depleted at baseline; therefore, a large potassium deficit likely exists, and aggressive replacement may be needed.

**Hypoglycemia**

- Hypoglycemia (defined as blood glucose <50 gm/dL) is important in the NCCU for several reasons:
  - It is known to cause direct neuronal cell injury due to alterations in metabolism; EEG changes can be seen at levels of 40 mg/dL, and the EEG begins to show suppression at 20 mg/dL; seizures may develop.
  - Hypoglycemia increases CBF which may be detrimental to patients with elevated ICP.
Thyroid disorders

- Thyroid-releasing hormone is secreted by the hypothalamus, which stimulates the anterior pituitary to release TSH (thyroid-stimulating hormone), which subsequently stimulates the thyroid gland to secrete T\(_3\), T\(_4\), and rT\(_3\).
- Free (non-protein bound) T\(_3\) is the active form of the hormone

Myxedema coma

- The most severe form of hypothyroidism, with mortality approaching 50–60% even after early initiation of treatment.
- Most likely to present in elderly women, but overall, a rare disease.
- Most likely scenario is a patient with stable hypothyroidism who develops one of these precipitating factors:
  - Hypothermia
  - Sepsis from any source
  - Stroke
  - Congestive heart failure
  - Pneumonia
  - Hyponatremia
  - Amiodarone exposure

Findings

- Slowly declining mental status that progresses from lethargy to coma
- Respiratory failure (carbon dioxide retention + hypoxemia)
- Possible airway edema
- Cardiac – nonspecific ST changes, bradycardia, decreased contractility, decreased cardiac output, and cardiomegaly
- Hyponatremia – kidneys are unable to properly secrete free water due to decreased GFR and increased vasopressin secretion
- Hypoglycemia, hypoxemia, and hyponatremia may result in reduced CBF and seizures
- Findings of chronic hypothyroidism are also likely to be present – dry skin, sparse hair, periorbital and pretibial nonpitting edema, macroglossia, moderate hypothermia, and delayed deep tendon reflexes

Diagnosis

- Diagnosis may be evident by physical findings consistent with hypothyroidism in the presence of stupor or coma and concomitant hypothermia
- Urinary sodium excretion is normal
- Elevated TSH and low total and free T\(_4\) and T\(_3\)
- Be wary of patients with suspected myxedema coma and normothermia; may actually represent a “fever” and may be a sign of associated sepsis, as these patients are usually hypothermic
Treatment

- Ventilatory support
- Cautious warming – rapid rewarming may result in vasodilation and refractory hypotension
- Glucocorticoid therapy (50–100 mg hydrocortisone q 6 h)
- Circulatory support with isotonic saline and vasopressors as needed
- Volume restriction versus hypertonic saline to treat the hyponatremia, depending on severity; sodium levels <120 meq/L are considered more severe
- Thyroid hormone therapy
  ▲ No optimal approach exists, although IV therapy is a common option
  ▲ High mortality of untreated myxedema coma must be considered versus risk of high-dose thyroid hormone therapy, which includes tachyarhythmias and myocardial ischemia

Hashimoto Encephalopathy

- Hashimoto encephalopathy is an autoimmune disorder that is related to Hashimoto thyroiditis
- Also known as STEAT (steroid-responsive encephalopathy associated with autoimmune thyroiditis)
- Antithyroid antibodies are present in both disorders; however, it seems that other unknown antibodies are actually responsible for the damage to the CNS in Hashimoto encephalopathy
- Disorder is uncommon and present more frequently in females

Findings

- Initial presentation is usually that of a rapidly progressive dementia similar to prion disease; however, the encephalopathy may present as delirium or psychosis with a gradual or subacute onset
- Seizures, rigidity, movement disorders, and myoclonus may also be present, although these symptoms may develop months after initial presentation of dementia

Diagnosis

- Antithyroid antibodies, including antithyroid peroxidase (also known as antimicrosomal antibody) and antithyroglobulin antibody will be present
- TSH may be normal or elevated
- Free $T_4$ may be normal or reduced
- No correlation between appearance of delirium or dementia and thyroid status
- EEG findings are similar to those of prion disease and include generalized slow-wave abnormalities
Pathology findings include widespread vasculitis of the CNS
MRI may show focal or diffuse nonenhancing abnormalities

Treatment

- Corticosteroids are effective in 50% of cases
- Immunosuppressants may be necessary for refractory cases

**Thyroid Storm**

- A severe form of thyrotoxicosis; the distinction between severe thyrotoxicosis and thyroid storm is somewhat subjective
- Mortality approaches 20–30%
- Most common etiology is Grave disease but may also occurs with solitary toxic adenoma or toxic multinodular goiter; exposure to iodine such as iodinated contrast or amiodarone may also precipitate thyroid storm

**Findings**

- CNS dysfunction
  - Agitation, delirium, lethargy, or psychosis
  - Progresses to seizures and coma
- Cardiovascular dysfunction
  - Dysrhythmia – frequently atrial fibrillation
  - Congestive heart failure
  - Tachycardia
  - Hyperdynamic contractility
  - Decreased systemic vascular resistance due to smooth muscle relaxation and release of nitric oxide from the endothelium
- Hyperthermia
  - Increased metabolic rate (increased CO₂ production/O₂ consumption)
- Gastrointestinal dysfunction
  - Nausea/vomiting
  - Jaundice
  - Hyperglycemia may be present
- Adrenocortical dysfunction
  - Thyrotoxicosis accelerates the metabolism of exogenous and endogenous cortisol
  - Given the degree of physiologic stress, a normal cortisol level may actually represent a relative adrenal insufficiency
Diagnosis

- Elevated free $T_4$ and free $T_3$ with decreased level of TSH (<0.05 $\mu$U/mL)

Treatment

- Goal of management is to stop synthesis and release of thyroid hormone and to block peripheral effects of the hormone
- A thionamide (propylthiouracil or methimazole) should be given first to inhibit thyroid gland synthesis
- Iodine therapy (potassium iodine) should be initiated no sooner than 30–60 min after thionamide therapy; iodine therapy inhibits release of thyroid hormone; however, if it is administered prior to thionamide therapy, it will actually stimulate the synthesis of new hormone, thus aggravating the condition
- Acetaminophen and active cooling to treat hyperthermia
- $\beta$ blockade effectively treats effects of $T_3$ on myocardial contractility
- Glucocorticoids (hydrocortisone 100 mg q 8 h)
  - Treats relative adrenal insufficiency if present
  - Provides some inhibition of peripheral conversion of $T_4$ to $T_3$
  - Avoid aspirin
  - Salicylates decrease protein binding of thyroid hormone, thereby increasing the free fraction of circulating hormone

Adrenal Crises (Acute Adrenal Insufficiency)

- Cortisol is the primary glucocorticoid in the body
- Corticoid-releasing hormone (CRH) is secreted by the hypothalamus and stimulates the anterior pituitary to release ACTH; ACTH subsequently stimulates the zona fasciculata of the adrenal gland to release cortisol
- Basal daily cortisol requirements = 15–25 mg hydrocortisone
- Cortisol requirements increase substantially under stress, trauma, or illness
- Cortisol is vital for cellular metabolism, homeostasis, and for the maintenance of vascular tone; insufficiency results in hypoglycemia and hypotension that is refractory to volume resuscitation and inotropic support
- This refractory hypotension can lead to decreased cerebral perfusion pressure
- Causes of adrenal insufficiency

- Primary (Addison disease)
  - Destruction of adrenal gland commonly by an autoimmune process
  - Absence of mineralocorticoid and glucocorticoid
  - If left untreated, patients present with profound adrenal insufficiency manifesting as hypotension, hypovolemia, and shock
Secondary (inadequate production of CRH or ACTH)

- Iatrogenic
  - Chronic suppression
    - Cortisol naturally participates in a negative feedback loop with ACTH secretion
    - Chronic administration of exogenous glucocorticoids results in adrenal gland atrophy and chronic suppression of the hypothalamus-anterior pituitary axis
    - The adrenal gland is then unable to mount an appropriate response to stress, resulting in profound hypotension, muscle weakness, and hypoglycemia
  - Etomidate
    - Etomidate directly inhibits cortisol synthesis by the adrenal gland; a single dose results in suppression for up to 12 h

- Chronic subclinical adrenal insufficiency
  - Chronic disease that is asymptomatic or presents with nonspecific symptoms such as weakness, dizziness, lethargy, or GI complaints
  - Manifests as refractory hypotension in the setting of physiologic stress or infection
  - Pituitary injury due to hemorrhage, ischemia, surgery, compression, or trauma

Diagnosis

- Random serum cortisol level
  - > 35 μg/dL is considered normal
  - <15 μg/dL is considered abnormal
  - 15–35 μg/dL may require corticotrophin stimulation test for further differentiation

Treatment

- “Stress-dose steroids” should be considered in any patient at risk for adrenal insufficiency or any patient with refractory hypotension despite volume resuscitation and vasopressor support
  - Regimens include
    - 100 mg hydrocortisone q 8 h
    - 10 mg dexamethasone q 8 h
  - In patients with severe sepsis or septic shock, current Surviving Sepsis Guidelines recommend initiation of 200–300 mg/day of IV hydrocortisone
therapy in 3–4 divided doses for 7 days in adult patients with hypotension refractory to adequate volume resuscitation and vasopressor therapy

Use of ACTH stimulation test to identify potential “responders” prior to initiation of corticosteroids is no longer recommended by the campaign

**Key Points**

- Acid-base disorders are commonly encountered in the NCCU
- Consequences of electrolyte derangement may become life threatening if unrecognized or persistently severe
- Derangements of serum sodium are common, and etiologies include SIADH, CSW, and DI
- Metabolic disorders and endocrinopathies may occur as comorbidities with any patient in NCCU and should always remain in the differential diagnosis of encephalopathy

**Suggested Reading**


Handbook of Neurocritical Care
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