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Chapter

Electrolytes in the ICU

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Abstract

Electrolyte disorders is an imbalance of certain ionized salts (sodium, potassium, calcium, bicarbonate, chloride) in the blood. Healthcare providers should be familiar with the principles of electrolyte physiology and pathophysiology. Disturbances in sodium homeostasis are primarily caused by volume abnormalities leading to primarily neurologic symptoms. Dyskalemias frequently present with cardiac manifestations therefore should be treated promptly before evaluating its cause. Ion deficiencies such as hypocalcemia, hypomagnesemia and hypophosphatemia should be corrected as they are associated with increased adverse events in critically ill patients.

Keywords: Electrolytes, Sodium, Potassium, critically ill, ICU

1. Introduction

Electrolytes are elements that naturally occur in the human body and help balance pH, facilitate passage of fluid through osmosis and regulate the function of neuromuscular, endocrine and excretory systems. Disturbances in these electrolytes are common clinical problems encountered in the intensive care unit with serious complications when they are depleted. Recent studies report that electrolyte imbalances are associated with increased morbidity and mortality. Possible mechanisms include damage to the kidney, activation of hormonal systems (such as RAAS) or the myriad of medication given in a critically ill patient. This chapter will focus on various electrolyte abnormalities seen in the critical care setting then touch on important ICU scenarios which could affect electrolytes.

2. Disorders of sodium homeostasis

- Serum sodium reflects the plasma tonicity and is inversely related to total body water. Changes in sodium are generally due to changes in total body water, not serum sodium, which regulates plasma tonicity and effective arterial volume. The body normally prevents plasma sodium to stray outside normal range (135 to 145 mEq/L or mmol/L) by controlling water intake and excretion.

- Sodium crosses systemic capillary membranes through clefts between endothelial cells therefore sodium concentration is identical in plasma and interstitial fluid [1]. Brain capillaries have tight endothelial junctions lined by astrocytic foot processes creating the blood–brain barrier which sodium cannot cross [2]. Consequently, an abnormal plasma sodium causes water movement across the blood brain barrier leading to either brain swelling or shrinkage.

- Osmoreceptors are hypothalamic neurons that are responsible for adjusting thirst and vasopressin secretion based on plasma sodium. Vasopressin binds to V2 receptors on the principal cells lining the renal collecting duct [3]. In the presence of vasopressin, water is allowed to flow out of the collecting tubule in the nephron attracted by a high solute concentration of the surrounding medullary interstitium. When plasma sodium is high, vasopressin levels are also increased.

2.1 Hyponatremia

2.1.1 Introduction

- Hyponatremia is defined as serum sodium below 135 mEq/L (135 mmol/L). It is the most common electrolyte disorder seen in clinical practice and the consequences can range from minor symptoms to life threatening complications including seizures and cardiorespiratory distress. 30% of critically ill patients have serum sodium<134 mEq/L [4]. Patients with hyponatremia are seven times more likely to die than those without hyponatremia during hospitalization [5].

- Hyponatremia can be classified based on temporality (acute <48 hrs; chronic >48 hrs) or based on serum sodium (mild 130-135 mEq/L (mmol/L); moderate 125-130 mEq/L (mmol/L); severe <125 mEq/L (mmol/L)) [6].

2.1.2 Presentation

- Patients with mild to moderate hyponatremia can present with nausea, confusion, headaches whereas moderate to severe hyponatremia can presenting with vomiting, cardiorespiratory distress, seizures and reduced consciousness [6].

- Patients are likely to present with severe symptoms if they have acute onset hyponatremia while chronic hyponatremia has a lower risk of neurological dysfunction as the brains counter-regulatory mechanisms [7].

2.1.3 Diagnostic approach

- The diagnostic approach of hyponatremia should follow a logical progression, answering several key questions. See **Figure 1**.

2.1.4 Treatment

- Treatment of hyponatremia is based on underlying pathogenesis.

- In patients who present symptomatically with hyponatremia, they should be considered as an emergency and given hypertonic therapy. 3% normal saline can be used, 150 ml over 20 min. Lab work should be obtained after hypertonic therapy is administered and the goal is to increase sodium by 3-5 mM which should improve patient's symptoms. If patients symptoms persist and sodium has increased by <4 mM then another round of hypertonic therapy can be given. If sodium increased by >6 mM and symptoms have not resolved, then further workup should be performed to check for alternative pathologies. Hypertonic bicarbonate has the same tonicity as 6% NaCl and is usually
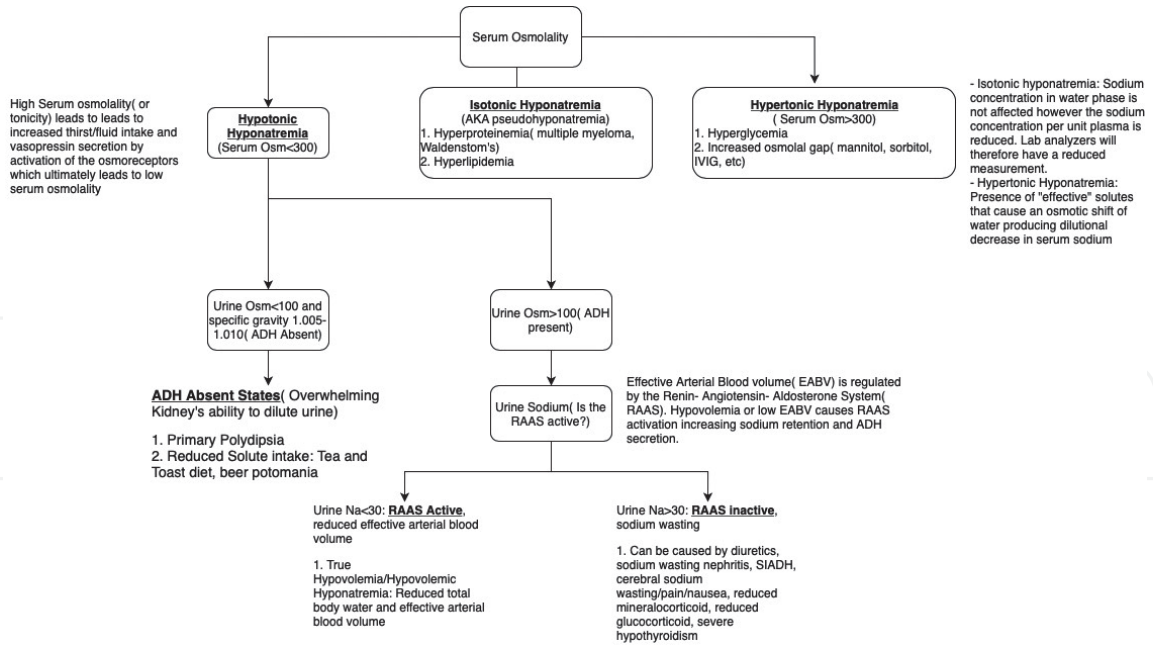
Figure 1.
Diagnostic approach to hyponatremia, starting with osmolality.

the fastest medication to obtain in an emergency. Typical dose of two ampules of hypertonic bicarbonate is equivalent to ~200 ml of 3% saline [8]. See **Figure 2**.

- Depending on the pathology, hyponatremia will be treated differently [9].

- In patients with ADH absent states, hyponatremia is caused because patient is drinking more fluid than the kidney can handle. In primary polydipsia, fluid restriction would be ideal [9].

- Normally the kidneys require solute to create urine therefore in patients with poor nutritional status, a normal amount of water/alcohol will cause hyponatremia. In patients with reduced dietary solute intake (such as chronic alcoholics), instituting a proper diet will correct hyponatremia. These patients can be given isotonic fluid is clinical evidence of hyponatremia [9].

- ADH absent states are high risk for over-correction therefore should be monitored closely.

$$Maximum\ Urine\ Output = \frac{Dietary\ Solute\ Intake}{Urine\ Osmolality} \qquad (1)$$

Normal diet contains 600-900 mosmol of solute/day and the minimum urine osmolality is 60 mosmol/kg therefore the maximum urine output (see Eq. 1) in a normal patient would be:

$$Maximum\ Urine\ Output = \frac{900}{60} = 15\ litres\ per\ day$$

Therefore, in patients with primary polydipsia, they will overcome the maximum urine output while patients with reduced solute intake will have reduced maximum urine output.
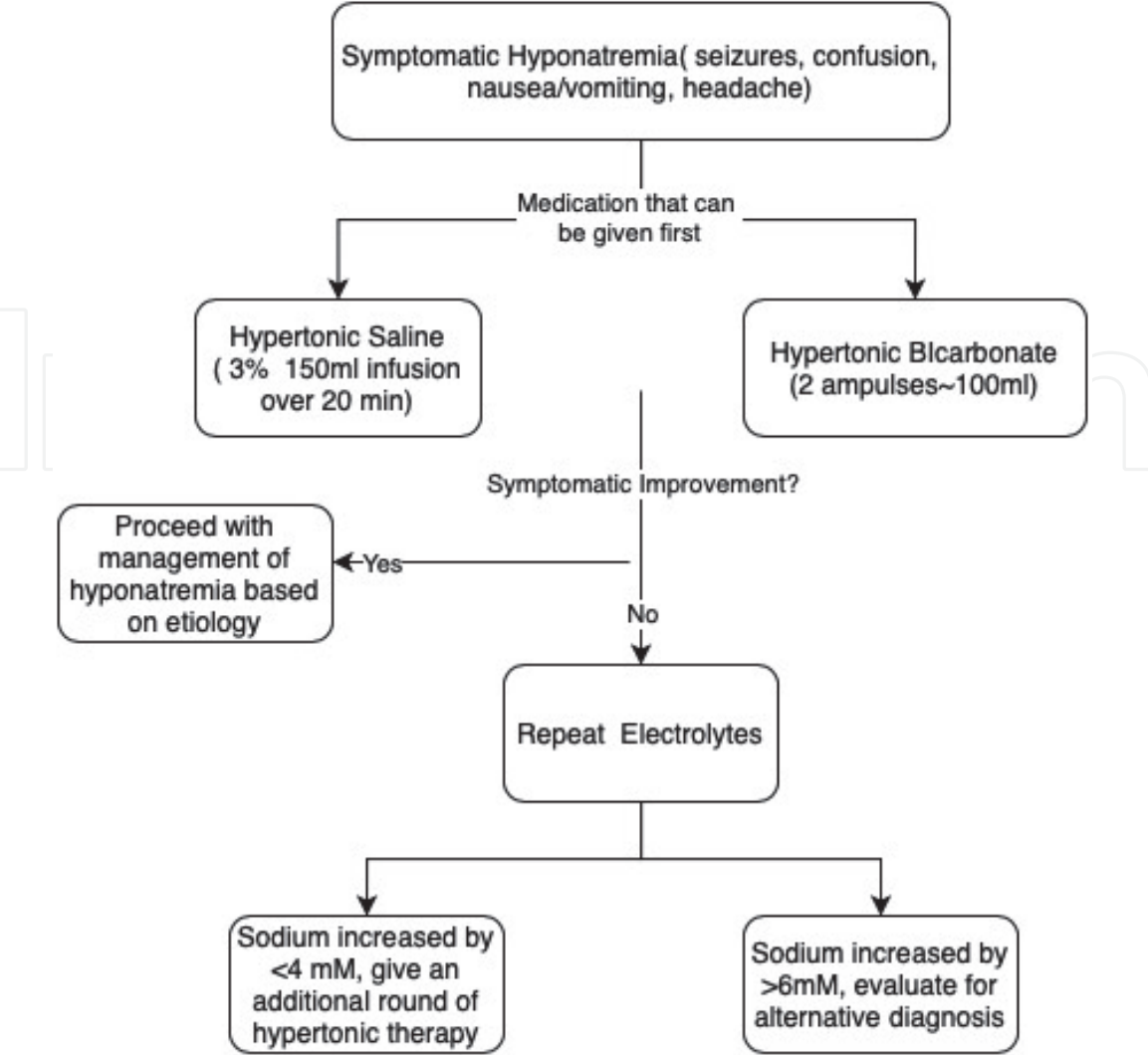
Figure 2.
Treatment algorithm for hyponatremia.

- In patients who have reduced EABV, treating the primary pathology will improve the serum sodium. History and physical examination is important when it comes to this patient population to effectively start correct treatment plan.

- In SIADH, the underlying cause should be treated concomitantly with initial treatment to raise serum sodium. Fluid restriction is the mainstay of therapy. In patients who have chronic SIADH, sodium or urea tablets can be used. Since patients with SIADH have a fixed urine osmolality, solute loads (such as urea and sodium tablets) are used to increase maximum urine output by increasing dietary solute [8, 9].

- In a patient who presents to the hospital with hyponatremia, it will be assumed to be chronic in nature. The target goal for these patients is 6-8 mEq/L (mmol/L) in a 24-hour period. Excessively rapid correction leads to osmotic demyelination syndrome.

- Common causes of hyponatremia overcorrection are:

  1. Treating the underlying cause

  2. Potassium Supplementation

3. Vaptans

- Risk factors for over-correction are cirrhosis, alcoholism, malnutrition and hypokalemia.

- Administration of potassium will also increase plasma sodium because it enters the cells, increasing intracellular osmolality and causing water to move from the extracellular space into the intracellular space, thus raising plasma sodium concentration

2.1.5 Overcorrection of sodium

- In a patient whose sodium was corrected outside 24 hour parameters can be started on rescue strategy. Desmopressin can be given (dose: 2mcg IV/subQ every 6 hours) to reduce free water output. Concomitantly, free water should be given (D5W at 6 ml/kg infused over 2 hours with labs after every infusion to determine rate of lowering) with the goal to bring sodium back within suitable levels for the next 24 hours. Once the sodium goal is achieved, the D5W can be stopped but desmopressin can be continued to prevent overly rapid correction [8, 9].

- Osmotic Demyelination syndrome: This syndrome usually has a delayed presentation 2-6 days after over-correction. Symptoms are dysarthria, dysphagia, paresthesia, quadriparesis and seizures. These symptoms are irreversible. MRI brain will show demyelinating lesions however may not appear for atleast 4 weeks after disease onset. Earlier detection may be possible with newer techniques such as DWI [8, 9].

2.2 Hypernatremia

2.2.1 Introduction

- Hypernatremia is defined as >145 mEq/L (mmol/L). This is often seen in hospitalized patients and is associated with increased mortality in patients [10–12]. Hypernatremia represents a deficit of water in relation to the body's sodium stores which can result from a net water loss or a hypertonic sodium gain.

2.2.2 Clinical presentation

- Most patients with hypernatremia are either very young or old [13]. Signs usually reflect central nervous system dysfunction. Elderly patients generally have few symptoms unless sodium exceeds 160 mEq/L [13, 14].

- Brain shrinkage induced by hypernatremia can cause vascular rupture, with cerebral bleeding, subarachnoid and permanent neurological damage. This is counteracted by a solute movement to the brain which normalizes the brain volume but does not correct hyperosmolality in the brain [15, 16].

- In patient with prolonged hyperosmolality, aggressive treatment with hypotonic fluids may cause cerebral edema [17, 18].

2.2.3 Diagnostic approach

- Net water loss accounts for a majority of cases of hypernatremia [19]. Since sustained hypernatremia can occur only when thirst or access to water is impaired, the groups at highest risk are patients with altered mental status, intubated patients and elderly individuals [20].

- Hypertonic sodium gain usually results from clinical interventions or accidental sodium loading. See **Figure 3** for diagnostic approach.

2.2.4 Treatment

- The treatment of hypernatremia requires addressing the underlying cause and correcting the prevailing hypertonicity.

- In patients who developed hypernatremia is several hours, rapid correction improves prognosis without increasing the risk of cerebral edema. The serum sodium can be reduced by 1 mEq/L (mmol/L) [16].

- A slower rate of correction is required in hypernatremia that lasted longer (≥2 days) or for unknown duration [21]. ln these patients, maximal rate of 0.5 mEq/L/hr. prevents cerebral edema and seizures [22, 23]. The goal of treatment is to reduce the serum sodium to 145 mEq/L.

- The preferred route of administering fluid is enterally however if not feasible then fluids should be given intravenously. Hypotonic fluids such as free water, 5% dextrose, ¼ isotonic saline and ½ normal saline can be used. The more hypotonic the infusate, the slower the infusion rate.

- Once the infusate is chosen, the free water deficit can be calculated (see Eq. 2) [24]:

$$Free\ Water\ Deficit = Total\ Body\ Water\% \times Weight(in\ kgs) \times \frac{Curent\ Sodium}{Ideal\ Sodium - 1} \quad (2)$$
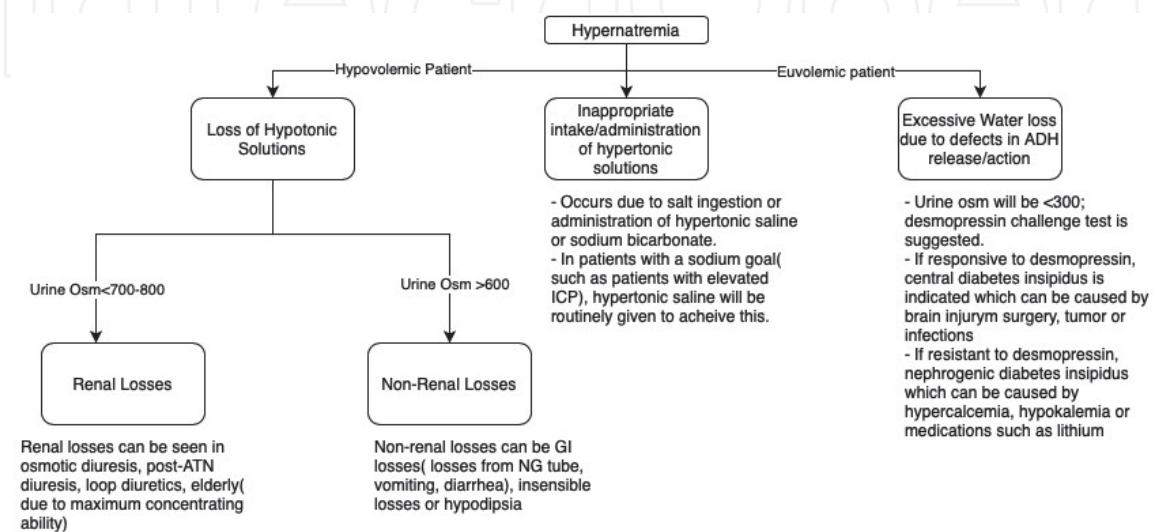
* TBW is:
Adult Male: 60%; 50% in elderly.

Figure 3.
Diagnostic approach for hypernatremia.

Adult Female: 50%; 45% in elderly.

- Through hospitalization, patients will have ongoing water losses which includes insensible losses (stool, sweat, respirations) and urine free water that should be accounted for. Insensible losses cannot be measured therefore can be approximated as 30-50 ml/hr [25, 26]. Urine free water can be calculated (see Eq. 3):

$$Urine\ Free\ Water\ clearance(ml/hr) = Urine\ flow\ rate$$
$$- \frac{Urine\ flow\ rate \times (Urine\ sodium + Urine\ Potassium)}{Serum\ Sodium} \quad (3)$$

- For acute or chronic hypernatremia, serum sodium should be measured every 4-6 hours and the estimated fluid replacement rate should be adjusted accordingly.

3. Potassium homeostasis

- Patients is an important electrolyte that has been proven essential for normal functioning of the cardiovascular system, skeletal muscle, internal organs and nervous system.

- The intracellular proportion of K+ represents 98% of the total body K+. The intracellular potassium concentration is approximately 140 mEq/L (mmol/L) compared to the normal serum potassium of 3.5-5.5 mEq/L (mmol/L). This ratio of potassium concentrations in the cells and extracellular fluid is a major determinant of the resting membrane potential across cell membranes [27].

- An abnormal potassium level predisposes patients to serious complications such as cardiac arrythmias, muscle weakness which could provoke sudden cardiac arrest or respiratory failure.

3.1 Hyperkalemia

3.1.1 Introduction

- Hyperkalemia is defined as serum potassium ≥5.5 mEq/L (mmol/L) which is commonly seen in patients with chronic kidney disease, diabetes or cardiovascular disease. High potassium intake is rarely sufficient to result in hyperkalemia [28].

- Based on the European Resuscitation Council Guidelines classification of hyperkalemia based on serum potassium levels [28]:

    1. Mild Hyperkalemia: - Serum Potassium 5.5-5.9 mEq/L (mmol/L)

    2. Moderate Hyperkalemia: - Serum Potassium 6.0-6.4 mEq/L (mmol/L)

    3. Severe Hyperkalemia: - Serum Potassium ≥6.5 mEq/L (mmol/L)

- Hyperkalemia is associated with increased mortality in patients with chronic kidney disease and ESRD on dialysis. See **Figure 4** for causes of hyperkalemia.
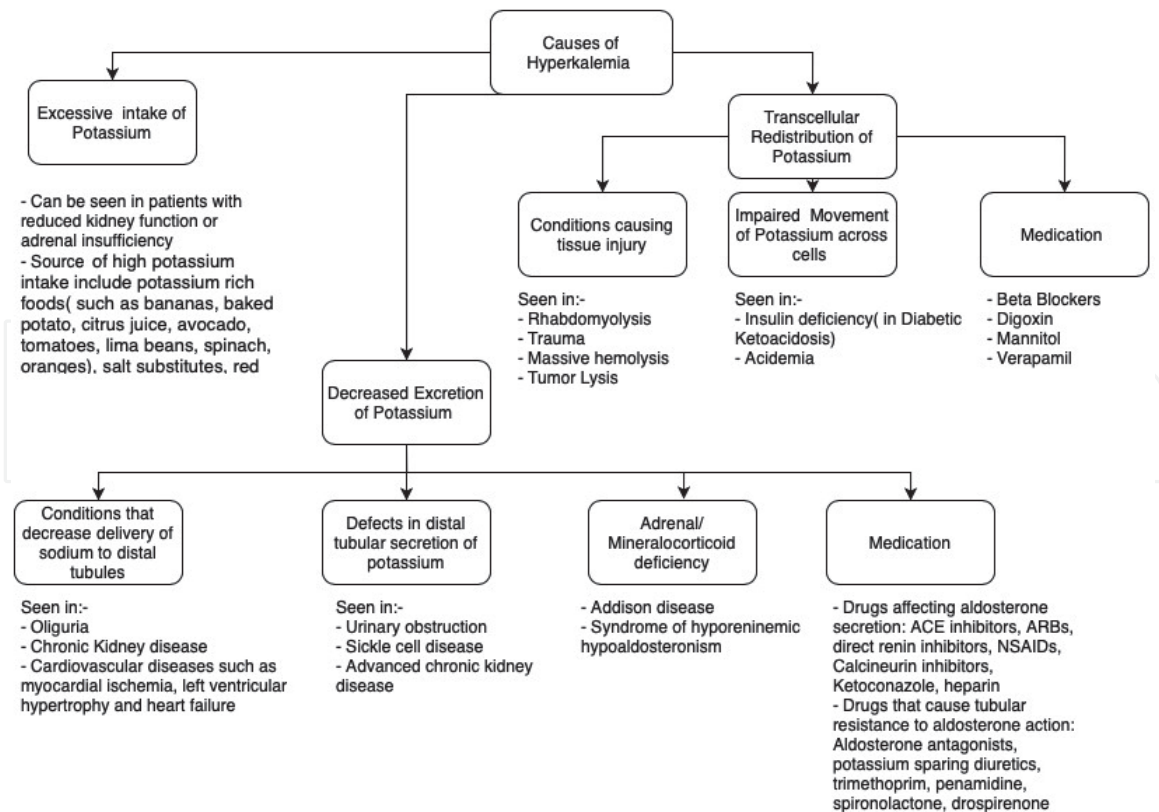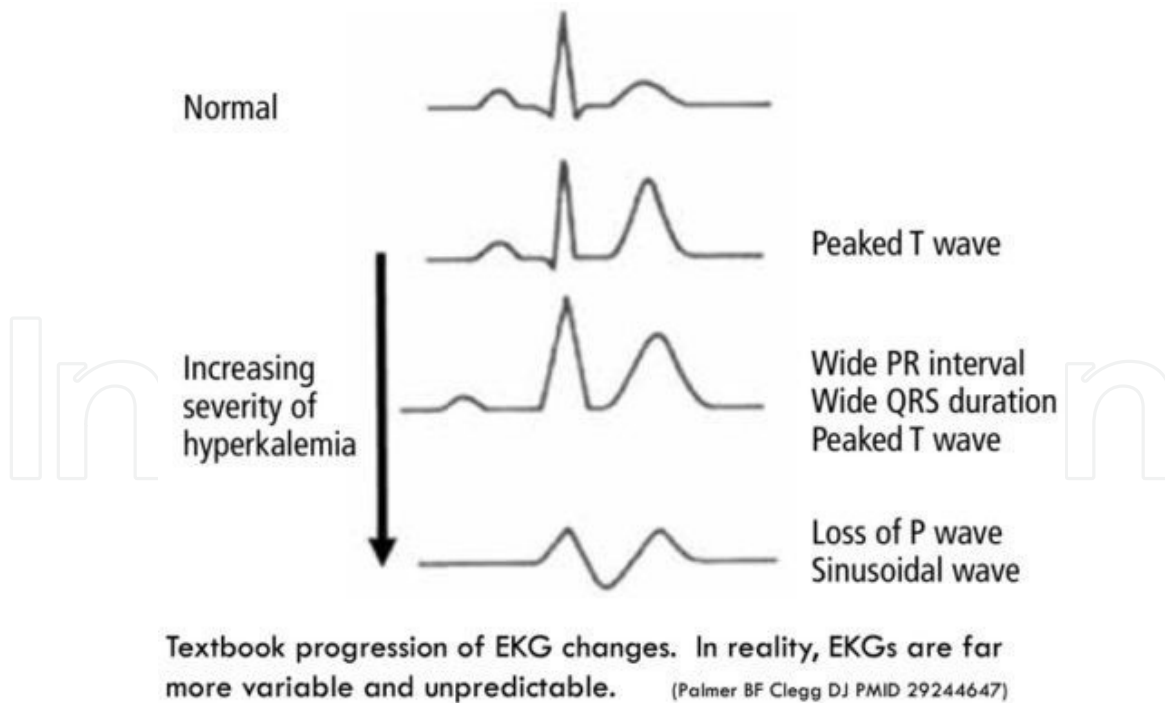
Figure 4.
Major etiologies of hyperkalemia.

3.1.2 Clinical presentation

- Hyperkalemia can manifest with neuromuscular weakness, bradycardia and ventricular tachycardia/fibrillation. In practice however, most patients are asymptomatic [28].

- Hyperkalemia is usually caused by increased potassium intake, decreased renal excretion and transcellular shift in potassium. The various pathologies that could lead to hyperkalemia can be divided based on underlying mechanism of cause:

- Pseudo-hyperkalemia refers to artificially elevated potassium which is seen in hemolysis, severe polycythemia and prolonged tourniquet application.

3.1.3 EKG findings

- EKG changes in hyperkalemia are seen with rising serum potassium levels (see EKG 1). Characteristically, there will be:

  1. Peaked T waves, best seen in the precordial leads

  2. Flattened P wave with prolonged PR interval

  3. Absent P wave

  4. Wide QRS and sine wave pattern

- There is a poor correlation between serum potassium levels and cardiac manifestations reported [28, 29].

Normal

Increasing severity of hyperkalemia

Peaked T wave

Wide PR interval
Wide QRS duration
Peaked T wave

Loss of P wave
Sinusoidal wave

Textbook progression of EKG changes. In reality, EKGs are far more variable and unpredictable. (Palmer BF Clegg DJ PMID 29244647)

EKG 1. EKG pattern showing changes in hyperkalemia.

3.1.4 Treatment

- Whenever hyperkalemia is seen on labs, and EKG should be done. If EKG changes are present or patient is symptomatic consistent with hyperkalemia, then this will confirm the diagnosis.

- In practice, most patients with hyperkalemia are asymptomatic (even with severe hyperkalemia).

- Potassium levels >6.5-7 (mmol/L) are more worrisome. Chronic hyperkalemia is better tolerated compared to acute which is more dangerous. Chronic hyperkalemia is seen in dialysis patients who are frequently hyperkalemic

- The acute management of hyperkalemia is the prevention or reversal of cardiac dysrhythmias. The primary goal of chronic treatment of hyperkalemia is to maintain serum potassium levels after acute treatment leads to reduction in serum potassium.

- Acute management of hyperkalemia [28, 30, 31]: See **Figure 5**.

- IV calcium gluconate is preferred over calcium chloride because calcium chloride causes skin irritation and extravasation which can lead to skin necrosis or thrombophlebitis. Peripherally, 3 g IV calcium gluconate can be given over 10 min. For central access, 1 g over 10 min or slow IV push can be done. Calcium lasts for 30-60 mins so it may need to be repeated.

- Regular insulin 10-20 units IV can be given with dextrose 25 g (when blood glucose <250 mg/dl). In patients with renal insufficiency, short acting insulin can be used. Insulin lasts for a few hours therefore may need to be re-dosed.

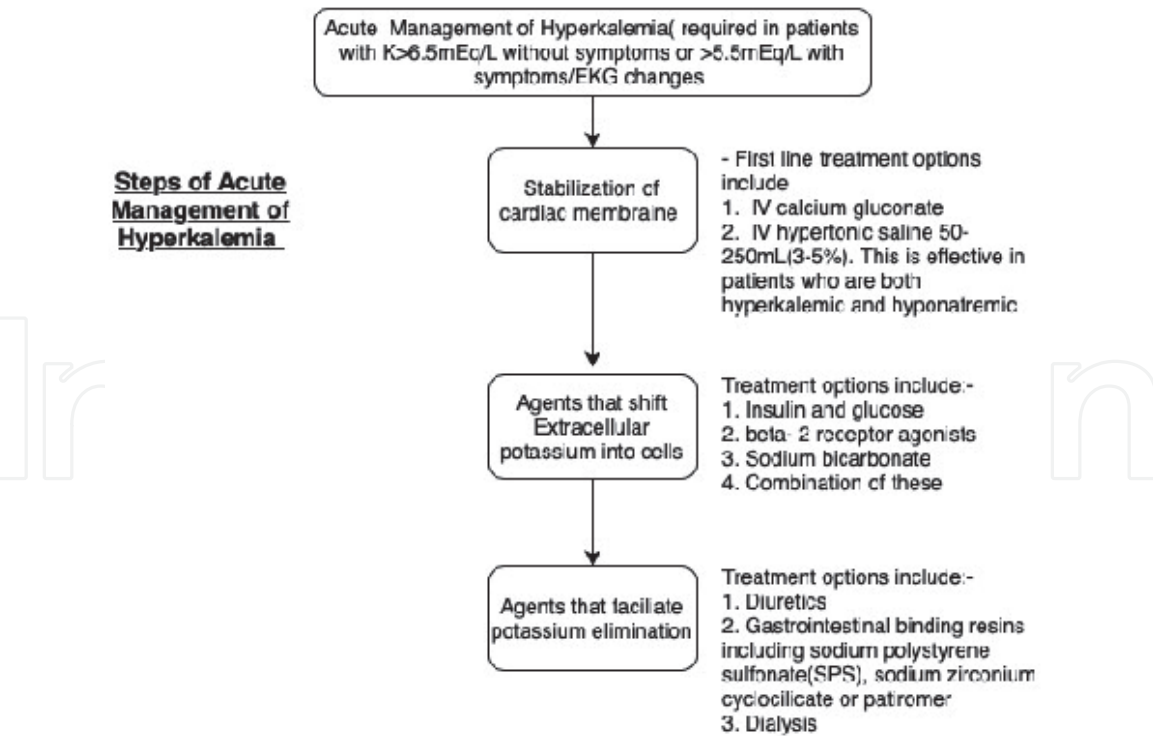- 10-20 mg albuterol can be given in normal saline over 10 min with nebulizer.

Figure 5.
Steps of acute management of hyperkalemia.

- Ultimately, patients will require elimination of excess potassium from the body (**Figure 6**).

- Diuresis with furosemide is suggested in hypervolemic/euvolemic patients able to produce urine. Furosemide increases urinary excretion of potassium which can be used in both acute and chronic management. Dialysis should be considered in patients who fail medical management, severe AKI/ESRD or persistent EKG changes.

- Chronic Management of hyperkalemia includes maintaining serum potassium after acute treatment [32].
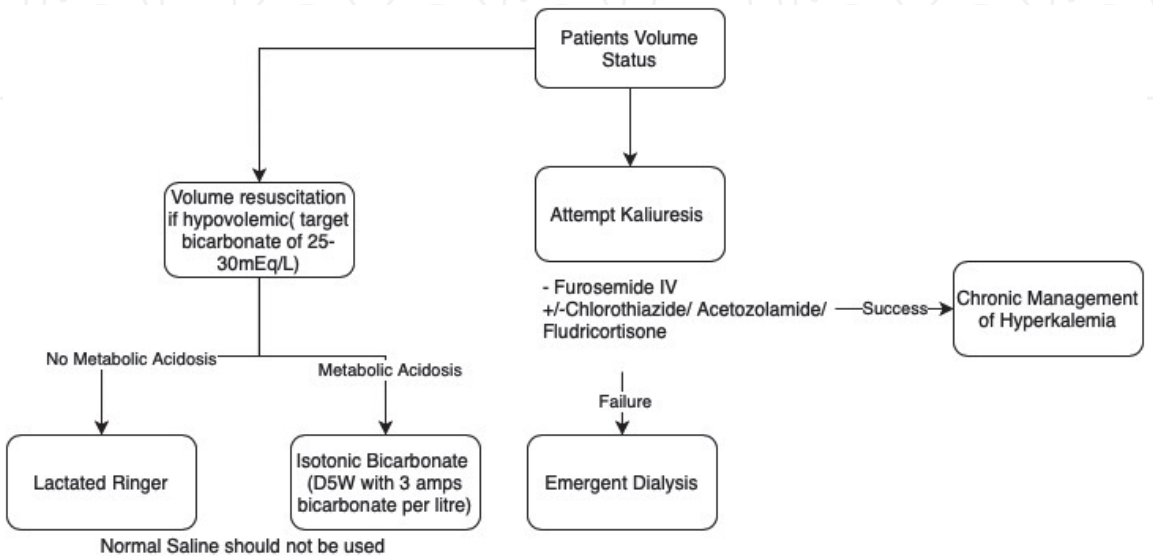

Figure 6.
Continued treatment of hyperkalemia.

- Treatment options include reviewing medication that can cause hyperkalemia, reduction in dietary potassium intake and start medication that can increase potassium excretion.

- Sodium zirconium cyclosilicate (Lokelma) should not be used for the acute management of hyperkalemia due to delayed onset of action. Onset of action is 1-6 hours with duration possibly 4-12 hours. Sodium polystyrene sulfonate (Kayexalate) has a high sodium load, and its time of onset is variable making it a poor choice for acute management.

3.2 Hypokalemia

3.2.1 Introduction

- Hypokalemia is a common electrolyte disorder defined as potassium <3.5 mEq/L (mmol/L) and can be life threatening if serum potassium <2.5 mEq/L (mmol/L). A vast majority of potassium is located intracellularly therefore hypokalemia is often due to a large total body potassium deficit [33].

- The relationship between potassium level and total body potassium deficit is exponential; as the potassium level falls progressively lower, this represents an exponentially larger decrease in the total body potassium deficit.

- Based on serum potassium, hypokalemia can be classified into:

  1. Mild Hypokalemia: - Serum Potassium 3-3.4 mEq/L (mmol/L)

  2. Moderate Hypokalemia: - Serum Potassium 2.5-2.9 mEq/L (mmol/L)

  3. Severe Hypokalemia: - Serum Potassium <2.5 mEq/L (mmol/L)

- Clinical features usually occur when serum potassium<2.5 mEq/L (mmol/L) and includes muscle pain, cramps, weakness, fatigue, constipation, syncope and palpitations [33, 34].

3.2.2 Diagnostic approach

- Hypokalemia can be caused by excessive potassium loss, inadequate intake or a transcellular shift of potassium.

- Inadequate potassium intake is a rare cause of hypokalemia and in most cases, dietary restrictions exacerbate hypokalemia due to other causes (see **Figure** 7) [33].

3.2.3 EKG changes

- EKG changes associated with hypokalemia are (see EKG 2) [33]:

  1. Decreased T wave amplitude

  2. ST-segment depression

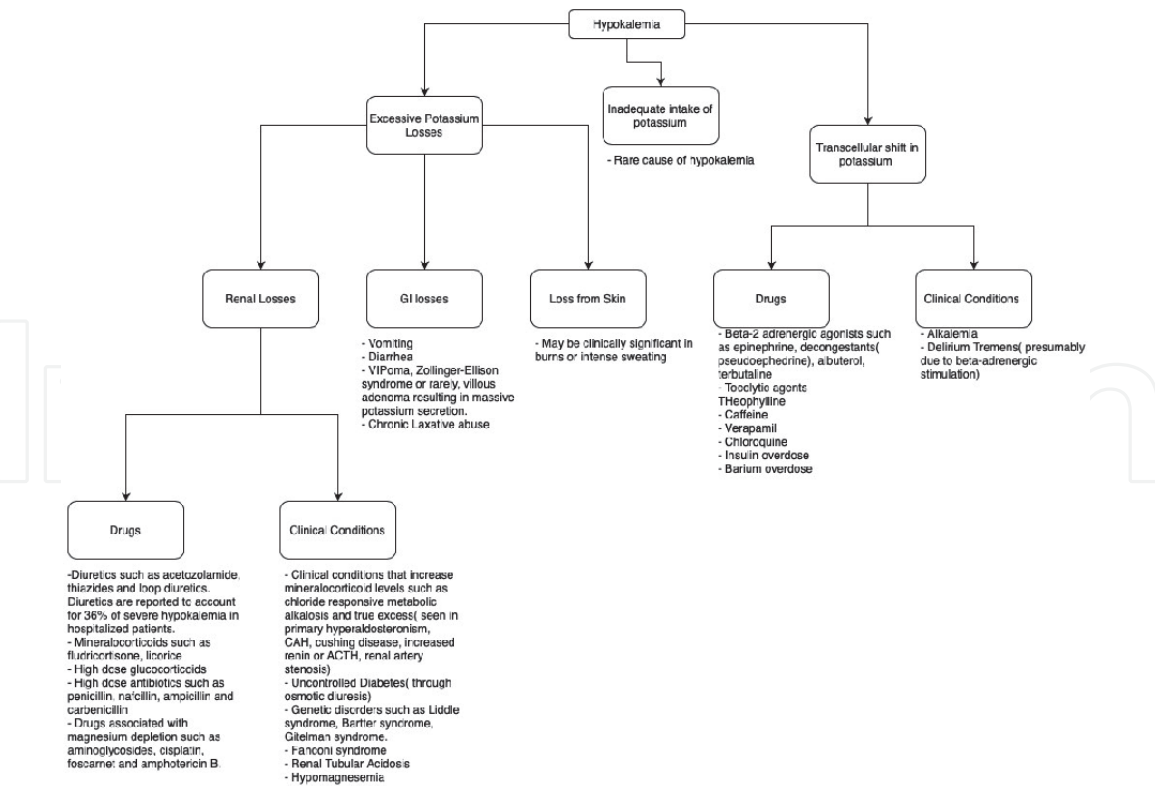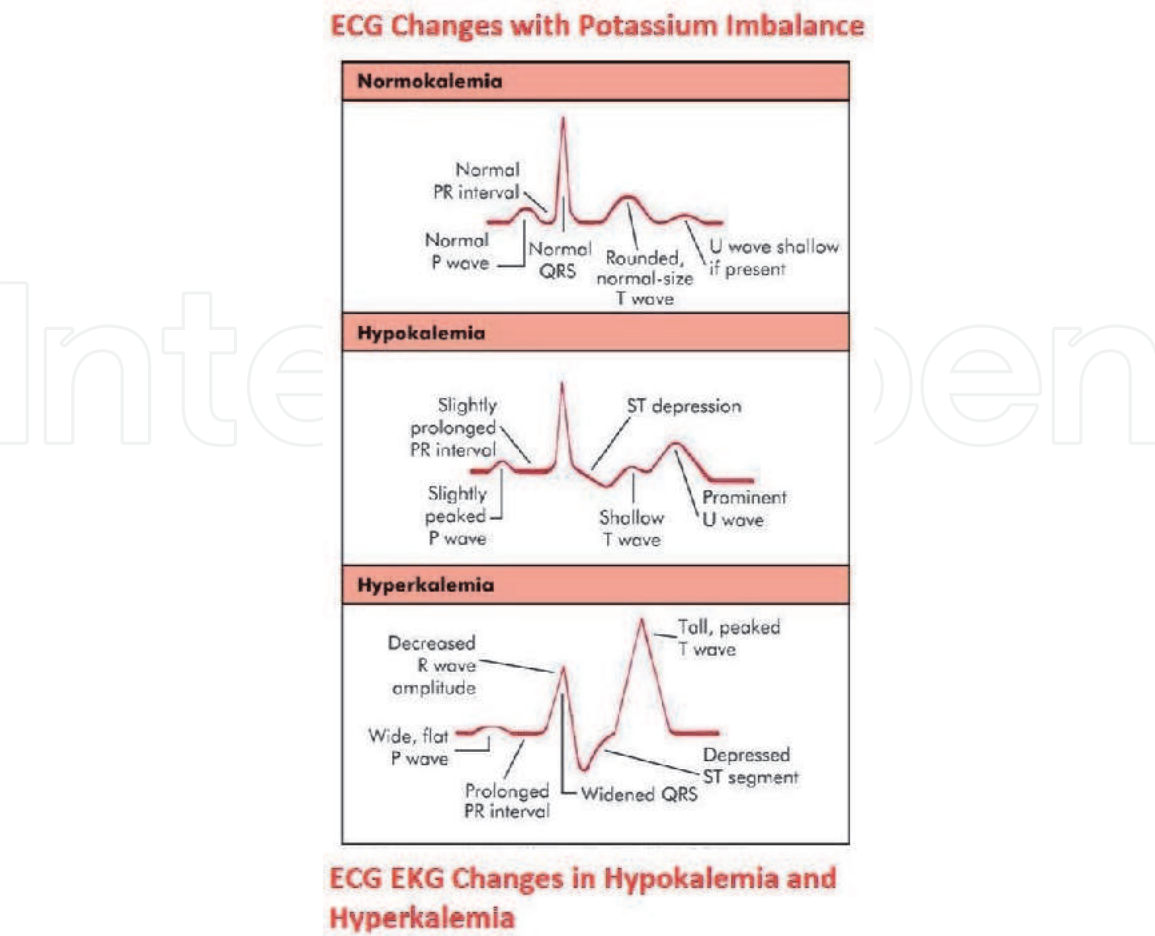 3. Presence of U wave (giant U waves may be mistaken for peaked T waves)

Figure 7.
Etiologies of hypokalemia.

4. Other findings include QT prolongation, ventricular extrasystoles, ventricular arrythmias.

EKG 2. EKG pattern showing changes in hypokalemia.

3.2.4 Treatment

- Goals of treatment are to reduce further potassium loss, replenish potassium stores, evaluate potential toxicities and treatment of the underlying cause [33–36].

- Due to the intracellular nature of potassium deficit means that intravascular potassium must be administered slowly, and time is required for potassium to enter the cells. Rapid administration may cause serum levels to be elevated even though there is a total body deficit leading to serum hyperkalemia.

- When treating hypokalemia, the goal potassium is >3.5 mEq/L (mmol/L). Traditionally, potassium goal >4 (mmol/L) was used to reduce the risk of arrythmias however larger studies have shown that the safest potassium level in myocardial ischemia is 3.5-4.5 (mmol/L) with evidence of higher/lower levels correlate with worse outcomes. In the specific case of DKA, with the absence of renal dysfunction, target potassium is >5.3 mEq/L (mmol/L).

- Enteral potassium repletion is preferred compared to IV route. Enteral potassium is cheaper, safer and does not irritate veins.

- Potassium chloride is the most commonly used formulation and are especially useful with metabolic alkalosis (increases serum chloride). Slow release formulations are suboptimal if immediate effect is desired however better tolerated. Another formulation is potassium citrate which may be useful in non-anion gap metabolic acidosis (the citrate will be converted into bicarbonate, thereby improving the acidosis).

- IV potassium can be used when there is lack of gut access/function, severe hypokalemia in need of emergent treatment or profound shock with severe hypokalemia. The rate of administration is 10 mEq/hour through a peripheral line or 20 mEq/hour through a central line. When IV repletion is >20 mEq/hour then continuous cardiac monitoring is suggested.

- Magnesium should be repleted as well because failure to treat this will make it difficult to fix hypokalemia. In patients with ongoing gastric losses, initiation of proton pump inhibitor may minimize electrolyte derangements.

4. Calcium and phosphate balance

- Calcium circulates in different forms. Within the plasma, 40% of calcium is bound to albumin while 15% is bound to citrate, sulfate or phosphate while 45% exists as physiologically ionized (or free) calcium. Total serum calcium is frequently misleading since it can vary based on albumin concentration and state of hydration [37].

- Plasma phosphorus exists as organic and inorganic forms. The inorganic forms are completely ionized circulating in the plasma. 99% of phosphate is present within cells.

- Only a small portion of total body calcium and phosphate is located in the plasma and it is the ionized calcium and inorganic phosphate that is regulated by hormones.

- Calcium balance is regulated by the parathyroid hormone and calcitriol which affects intestinal absorption, bone formation/ resorption and urinary excretion. Phosphorus balance is primarily regulated by the parathyroid hormone [38].

- Most of the body's calcium as well as phosphate exists in bone which functions as a reservoir to maintain normal plasma ionized calcium and phosphate concentration.

- Ionized calcium is the best measurement of biologically active calcium in critically ill patients.

4.1 Hypocalcemia

- Common electrolyte abnormality defined as ionized calcium level < 4.4 mg/dl or total calcium level < 8.4 mg/dl (corrected by albumin). Critically ill patients are commonly affected. Ionized calcium <0.65 is critically low which could cause hypotension.

4.1.1 Clinical presentation

- Clinical presentation of hypocalcemia can vary from asymptomatic to severe symptoms. Acute hypocalcemia can present with neuromuscular irritability (with numbness/tingling of perioral region, fingers/toes), myalgias, muscle cramps/spasms or tetany.

- Chronic hypocalcemia (develops over years) is often asymptomatic however still possible to cause neuromuscular irritability.

- Trousseaus sign is a hallmark sign of acute hypocalcemia in which 94% of patients will have a positive sign [39].

- EKG changes that are seen in hypocalcemia are

    1. QT segment prolongation or ST segment lengthening

    2. AV conduction block

    3. Acute anteroseptal injury without myocardial infarction

    4. Abnormal T waves

4.1.2 Diagnostic approach

- When considering treating hypocalcemia, always confirm with ionized calcium, magnesium and phosphate. Magnesium abnormalities can lead to functional hypoparathyroidism.

- Calcium should also be corrected based on serum albumin.

- Various causes of hypocalcemia are

    1. Medications: - Anticonvulsants (phenytoin, phenobarbital, carbamazepine), antibiotics (rifampin, aminoglycosides, foscarnet), loop

diuretics, chemotherapy (cisplatin, 5-fluorouracil) and drugs that inhibit bone reabsorption (bisphosphonates, calcitonin and denosumab)

2. Severe Inflammation seen in sepsis or major buns

3. Pancreatitis (especially in hypertriglyceridemia induced pancreatitis)

4. Increased Citrate:- Seen in massive transfusion, plasmapheresis, leukapheresis and renal replacement therapy.

5. Alkalosis

6. Chronic conditions such as hypoparathyroidism, Vit D deficiency or osteoblastic metastasis.

7. Chronic Kidney disease (most common cause)

- Most critically ill patients have hypocalcemia and treatment is usually not indicated. Treatment is indicated when patient is symptomatic, presence of prolonged QT interval or severe hypocalcemia (ionized calcium < 0.8) [37, 39].

- IV calcium can be used in symptomatic/severe cases or in the presence of EKG changes. IV formulations are calcium chloride (central access) and calcium gluconate (peripheral access). Both are equally fast however calcium chloride can cause tissue necrosis if it extravasates.

- First, IV loading dose can be given (1 g calcium chloride or 2-3 g calcium gluconate) followed by maintenance doses if there is an ongoing process with smaller doses (for example calcium gluconate 1 g q1h as needed). IV calcium increases ionized calcium in patients with hypocalcemia, but randomized trials have not evaluated effect on clinical outcomes [40]. IV calcium can eventually be transitioned to oral formulations.

- For mild- moderate hypocalcemia, therapy can be started with oral calcium. Usual dose is calcium carbonate 1 g every 12 hours.

- Treatment of hypocalcemia is contraindicated in hyperphosphatemia (could cause precipitation of calcium phosphate, calciphylaxis), ethylene glycol poisoning (calcium promotes calcium oxalate precipitation in the brain) and digoxin poisoning (theoretical contraindication).

4.2 Hypercalcemia

4.2.1 Introduction

- Hypercalcemia is a serum calcium>10.5 mg/dl or ionized calcium>5.6 mg/dl. Calcium is partially bound to albumin therefore should be adjusted based on albumin. Only ionized calcium is biologically active so, if available, ionized calcium should be used to manage hypercalcemia among critically ill [41].

- Hypercalcemia can be classified based on severity:

1. Mild Hypercalcemia:- Total calcium 10.5-12 mg/dl or ionized calcium 5.6-8 mg/dl

2. Moderate Hypercalcemia:- Total calcium 12-14 mg/dl or ionized calcium 8-10 mg/dl

3. Hypercalcemic Crises:- Total calcium >14 mg/dl or ionized calcium >10 mg/dl.

4.2.2 Clinical features

- Mild hypercalcemia may be asymptomatic however rapid increases are more likely is be associated with symptoms than chronic hypercalcemia.

- This can present as bone pain, delirium (which could progress to stupor/coma), paresthesia, muscle weakness, GI symptoms (abdominal pain, pancreatitis, constipation, ileus, nausea/vomiting).

- Hypercalcemia does not commonly affect EKG or cardiac function however short QT interval may be a common finding.

4.2.3 Diagnostic approach

- Various causes of hypercalcemia are:

    1. Hyperparathyroidism (Primary and tertiary)

    2. Malignancy: Approximately 80% of these cases are caused by increased PTH-related peptide (most often squamous cell carcinoma of lung/head/neck) which is a protein that mimics PTH. 20% of cases is due to direct bone invasion.

    3. Medications: - Vit A/D excess, increased calcium intake (milk-alkali syndrome, chronic renal failure), teriparatide, lithium, thiazide diuretics, TPN

    4. Granulomatous diseases:- Such as sarcoidosis, TB, fungal infections

    5. Rhabdomyolysis

    6. Addison's disease

    7. Paget's disease

4.2.4 Treatment

- Overall, almost 90% of hypercalcemia is due to primary hyperparathyroidism or malignancy.

- Factitious Hypercalcemia may also occur when total calcium is elevated but ionized calcium is normal. This occurs when serum albumin or protein levels are elevated.

- Initial volume resuscitation is essential since hypercalcemia typically causes volume depletion due to enhanced fluid excretion by the kidneys and reduced oral intake. Plasmalyte is a good choice since it is a balanced crystalloid which does not contain calcium. Lactated ringer contains calcium and normal saline can cause acidosis (possibly increasing risk of renal injury) therefore both are suboptimal compared to plasmalyte (see **Figure 8**).

- Mild to moderate hypercalcemia without symptoms does not require aggressive treatment. The underlying disease should be treated, and potentially contributing medication discontinued. Immobility may exacerbate hypercalcemia therefore patients should be mobilized.

- In patients with severe hypercalcemia, IV fluid hydration (at least 2-4 L/day for 1-3 days) should be given in association with bisphosphonates and calcitonin to reduce serum calcium levels.

- Bisphosphonates block calcium release from bones causing unidirectional uptake by the bones. These take days to work and should be started early. Bisphosphonates should be avoided in patients with increased calcium intake (milk-alkali syndrome. The main side effect is renal failure however the most common is flu-like syndrome which can be treated symptomatically. Various options are pamidronate 60-90 mg IV or zoledronic acid 4 mg IV [41, 42].

- Calcitonin is an excellent agent to control severe symptomatic hypocalcemia while waiting for bisphosphonates to take effect. These work by reducing bone calcium reabsorption and cause a temporary reduction in calcium. Calcitonin can cause nausea, vomiting and flushing. For adults, calcitonin 4 U/kg
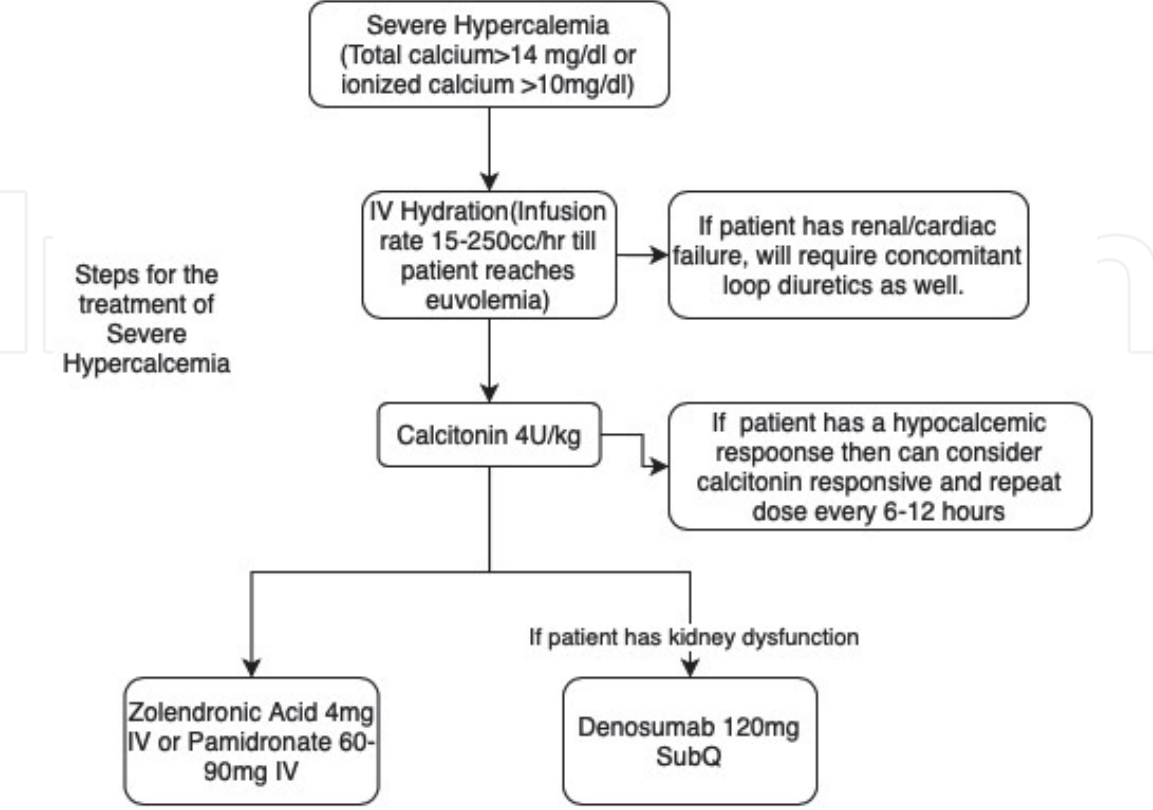

Figure 8.
Treatment of hypercalcemia.

subcutaneously every 12 hours for 24 hours; effect of calcitonin is short lived, and tolerance typically develops within 2 days [43].

- In patients who bisphosphonates and calcitonin are ineffective, denosumab (monoclonal antibody that inhibits osteoclast formation and bone resorption) can be considered.

- Loop diuretics can be used once volume status normalizes to enhance calcium excretion and to avoid volume overload. They may have to be started earlier if patient has a history of congestive heart failure or kidney disease. Glucocorticoids can be given in patients with granulomatous disease, Vit D overdose or malignancy to inhibit conversion of Vit D to calcitriol.

- In renal failure, dialysis with low calcium bath is an option.

4.3 Hyperphosphatemia

- Hyperphosphatemia is defined as serum phosphate >4.5 mg/dl in adults.

- Hyperphosphatemia is itself, asymptomatic however can indirectly cause symptoms by causing symptomatic hypocalcemia (by binding to calcium) or calciphylaxis (precipitation of calcium phosphate in tissues which can manifest as skin ulceration).

- Sustained hyperphosphatemia generally occurs in renal failure since normally the kidneys are efficient in phosphate excretion. Possible inciting events are [44]

   1. Tissue necrosis: Tumor lysis syndrome, rhabdomyolysis, hemolysis, fulminant hepatitis, severe hyperthermia

   2. Endocrinopathy: Hypoparathyroidism, hypothyroidism/ hyperthyroidism, adrenal insufficiency, acromegaly

   3. Medications: Exogenous phosphate intake (phosphate containing laxatives/enemas, TPN), Vit D toxicity, bisphosphonates, fosphenytoin

- False elevation of phosphate can be seen in hyperlipidemia, hyperbilirubinemia, hyperglobulinemia (multiple myeloma) or a hemolyzed specimen.

- Calcium phosphate product (see Eq. 4) can predict the risk of calciphylaxis and is more important than the phosphate level alone. Calcium-phosphate product>70 causes an increased risk of calciphylaxis.

   Calcium Phosphate Product = Serum Calcium x Serum Phosphate (4)

- Acute treatment of hyperphosphatemia (see **Figure 9**) includes treating inciting event, phosphate restricted diet, fluid resuscitation and forced diuresis (acetazolamide+ − furosemide) or dialysis [44].
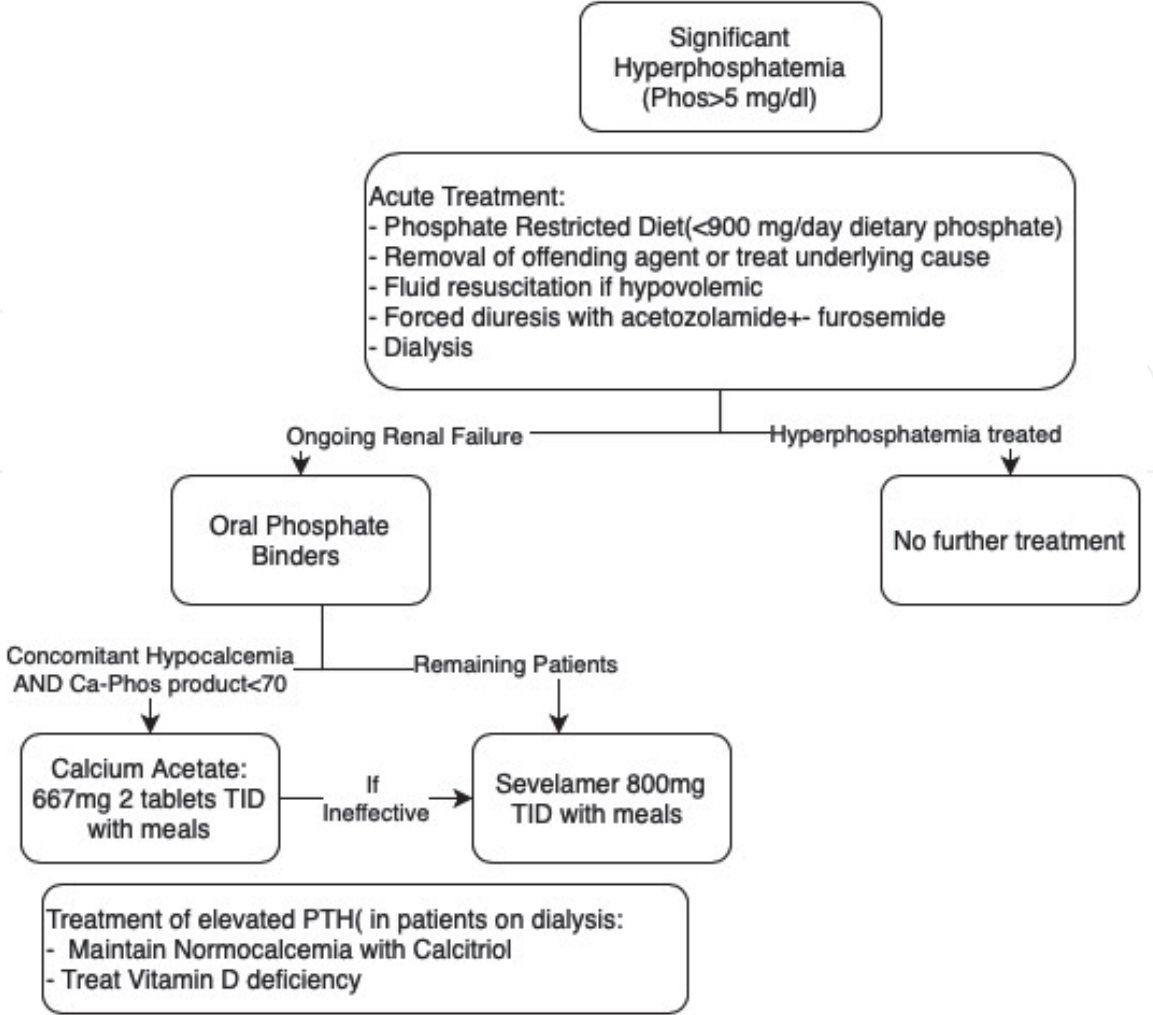
Figure 9.
Treatment of hyperphosphatemia.

- If patient has persistent renal failure, can start oral phosphate binder. Calcium acetate can be useful in patients with concomitant hypocalcemia and should be avoided in patients with hypercalcemia, Vitamin D toxicity and Ca-Phos product>66. Sevelamer is a nonabsorbable resin that is preferred for patients on dialysis [44].

4.4 Hypophosphatemia

- Hypophosphatemia is defined as serum phosphate <2.5 mg/dl.

- Patients with hypophosphatemia can present with paresthesia, tremors, seizures, impaired heart contractility, arrythmias, muscle weakness (including the diaphragm). Usually, symptoms occur at levels <1-2.5 mg/dl. Most cases of mild (or even moderate) hypophosphatemia are asymptomatic.

- Causes of hypophosphatemia are [45]:

    1. Shifting phosphate into cells: Diabetic ketoacidosis, refeeding syndrome, respiratory alkalosis, hungry bone syndrome

2. Reduced GI uptake: Inadequate oral intake, chronic diarrhea, drugs (chronic use of antacids containing calcium, magnesium or aluminum).

3. Increased Renal losses: Diuretics (loop diuretics, acetazolamide, thiazides), osmotic diuresis, auto-diuresis (post-ATN, iatrogenic volume overload), CRRT, hyperparathyroidism, other medications (aminoglycosides, IV iron, tenofovir, chemotherapeutic agents).

4. Multifactorial: Alcoholism, Vitamin D deficiency, critical illness (sepsis, trauma, major surgery, burns).

5. Potential causes of pseudo-hypophosphatemia are hyperbilirubinemia, mannitol, paraproteins and acute leukemia.

- Generally, hypophosphatemia can be determined by history and review of labs/medication. Fractional excretion of phosphate can be helpful in cases when cause is unclear. Fractional excretion of phosphate should be <5% as a normal response to hypophosphatemia however >5% can be seen in renal phosphate wasting [45, 46].

- IV phosphate can be given for severe hypophosphatemia, symptomatic, or in patients with lack of enteral access or malabsorption. These should be infused slowly since rapid infusion can lead to transient hyperphosphatemia (leading to hypocalcemia). Either potassium or sodium phosphate can be used.

- Oral phosphate can be given however tends to cause diarrhea. It is available as Phos-NAK packets (which contains 8 mM phosphate, 7 mEq potassium and 7 mEq sodium), oral sodium phosphate liquid and oral potassium phosphate liquid [47].

  o Phosphate ≤1.5 mg/dl:- Orally, 16 mM phosphate every 6 hours. Intravenously, initial dose can be 30 mM infused over 4 hours

  o Phosphate >1.5 mg/dl:- Orally, 8 mM phosphate every 8 hours. Intravenously, initial dose of 15 mM phosphate can be infused over 2 hours.

- Patients with active refeeding syndrome and morbid obesity, can consider using higher doses than indicated based on phosphate levels.

5. Magnesium homeostasis

- Magnesium is the 4th most abundant cation in the body. Magnesium homeostasis needs to be tightly regulated and thus facilitated by intestinal absorption and renal excretion. Magnesium plays an essential role in bone formation, neuromuscular stability and muscle contraction.

5.1 Hypomagnesemia

- Magnesium <1.8 mg/dl is defined as hypomagnesemia. Reported prevalence of hypomagnesemia ranges from 2.5-15% in the general population however higher in the ICU setting.

- Most patients are asymptomatic until concentration is <1.2 mg/dl however presentation can overlap with other abnormalities. Patients can present with nausea/vomiting, loss of appetite, neuromuscular irritability, tremors/tetany, hypocalcemia, hypokalemia, seizures, psychosis and arrythmias [48].

- Hypomagnesemia induced EKG changes include:

    1. Flattened T wave and U waves

    2. Prolonged QT interval and widened QRS complex

    3. Prolonged QT interval

- Causes of hypomagnesemia are:

    1. Medications: - Diuretics (except potassium sparing diuretics), antibiotics such as aminoglycoside, amphotericin and pentamidine, cyclosporine and tacrolimus, platinum based chemotherapy and proton pump inhibitors

    2. Hypercalcemia, hyperphosphatemia, metabolic acidosis

    3. Renal disease: - Post-ATN diuresis, osmotic diuresis, renal tubular acidosis

    4. GI Losses: - Malabsorption, diarrhea/vomiting, pancreatitis

    5. Chronic alcoholism, diabetes, large volume transfusion of citrated blood products, sepsis

- Magnesium repletion is generally safe except for myasthenia gravis (due to increased risk of muscle weakness) and renal failure.

- For patients with mild hypomagnesemia (1.5-2 mg/dl), oral magnesium can be used. Oral formulations are magnesium oxide 400 mg twice a day or magnesium hydroxide milk of magnesia) 15 ml once daily. If unable to take PO medication, 2 g of IV magnesium sulphate can be given.

- For moderate hypomagnesemia (1.2-1.5 mg/dl), intermittent infusions of 2-4 g magnesium sulphate IV can be given. To improve intracellular absorption, the dose can be infused for a longer period of time.

- For severe hypomagnesemia (<1.2 mg/dl), multiple doses of IV magnesium can be given or a continuous infusion of IV magnesium (4-8 g IV magnesium sulphate over 24 hours) (see **Figure 10**).

- 1 g magnesium sulphate is equivalent to 100 mg of elemental magnesium.

- In Torsade de Pointes or seizures secondary to hypomagnesemia, patients can be loaded with 2 g magnesium sulphate over 5-15 min followed by 2 g additionally over 30-60 min. These are followed by a continuous infusion of magnesium sulphate 1 g/hour. If the magnesium level is 5-7 mg/dl, the infusion should be reduced by 50%. If magnesium is >7 mg/dl then the infusion should be stopped.
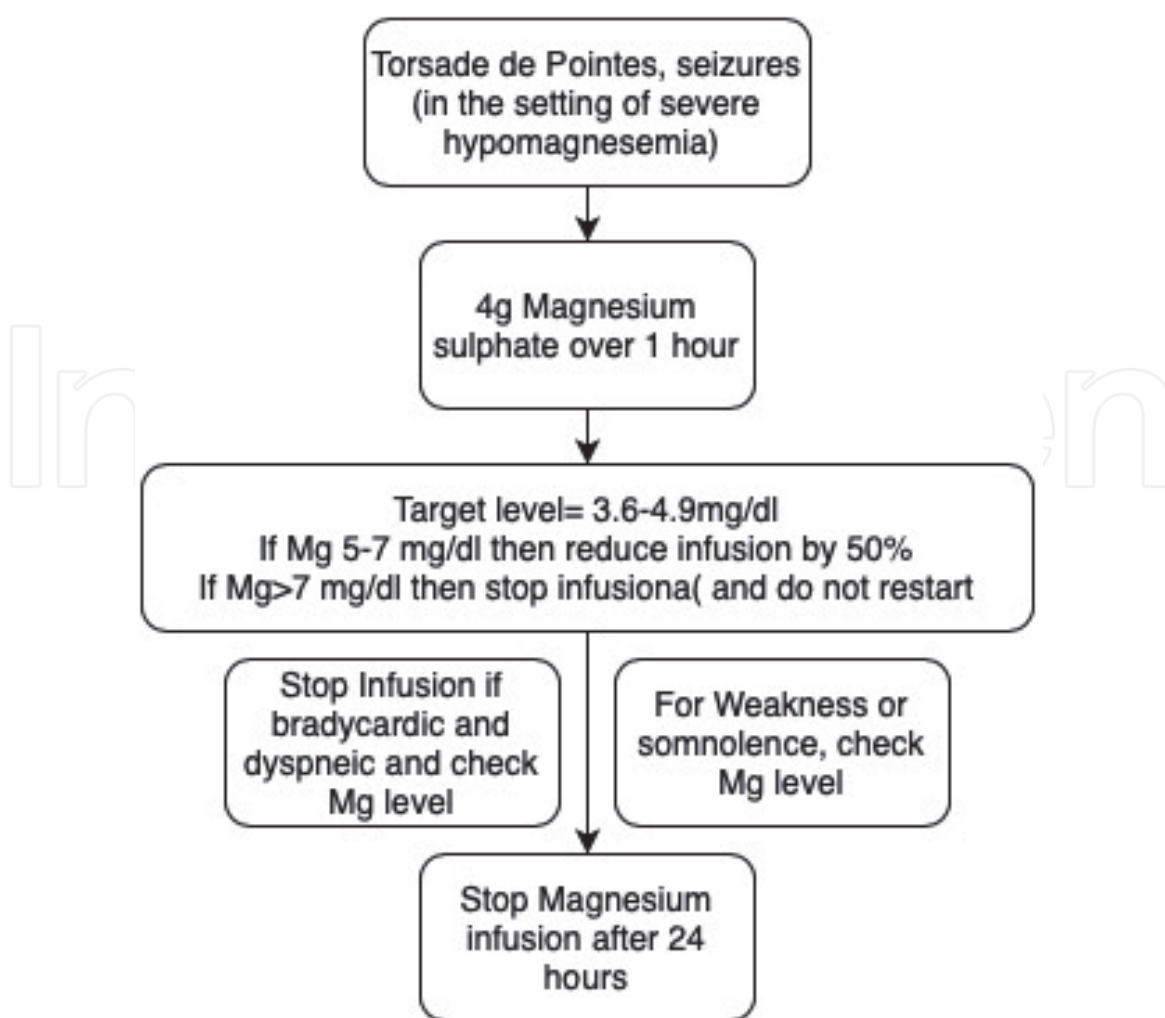
Figure 10.
Treatment of severe symptomatic hypomagnesemia.

5.2 Hypermagnesemia

- Magnesium>2.6 mg/dl is defined as hypermagnesemia. Patients with serum magnesium<4.8 mg/dl are usually asymptomatic, deep tendon reflexes may be diminished with serum magnesium>6.1 mg/dl and absent when >12 mg/dl [48].

- Patients can present with lethargy, confusion, nausea, vomiting, bradycardia. In severe cases, muscle weakness, respiratory distress, apnea, heart block, severe bradycardia, delirium and coma [48].

- EKG will show widened QRS complex with peaked T waves. Heart block can also be seen.

- Renal failure is required in addition to another source of magnesium to cause persistent hypermagnesemia. Concomitant causes of hypermagnesemia are:

    1. Exogenous magnesium:- Magnesium infusion for pre-eclampsia, magnesium containing antacids and magnesium containing laxatives/enema

    2. Endogenous magnesium from cellular lysis:- Rhabdomyolysis, hemolysis, tumor lysis syndrome and crush injury, severe burns.

- In most cases of hypermagnesemia, discontinuing magnesium containing drugs or supplements or volume replacement can sufficiently treat it [48].

- In patients with moderate hypermagnesemia (3.6-10 mg/dl or no cardiac/respiratory symptoms), the underlying cause should be treated. Furosemide can be used to enhance magnesium excretion.

- In patients with severe hypermagnesemia (causing cardiac/respiratory symptoms), IV calcium is required to stabilize the myocardium (2 g of calcium gluconate IV over 5-10 min followed by a continuous infusion in severe cases). In patients who are non-oliguric, furosemide with IV fluids can be used for elimination of magnesium. In patients who are oliguric, emergent dialysis is required.

6. Common conditions in the ICU

6.1 Massive transfusion protocol

- Massive transfusion protocol should be used in critically ill bleeding patients anticipated to require massive transfusion.

- Two common electrolytes that occur during MTP are hypocalcemia and hyperkalemia.

- Hypocalcemia is caused by the presence of the anticoagulant citrate (each bag on pRBC contains 3 g citrate). Normally, this amount can be rapidly cleared by the liver however in critically ill patients receiving multiple units, the process of liver elimination is compromised. Citrate accumulates in the blood where it binds to circulating ionized calcium thereby causing hypocalcemia [49].

- Bedside measurement of calcium can be used to guide calcium management. When administering MTP (around 6 units pRBC), it is reasonable to administer 3 g calcium gluconate.

- Hyperkalemia has been shown to be a risk when patients are transfused >7 units of pRBC [50]. This can be exacerbated in patients with renal failure, effective circulating volume depletion or more commonly hypoaldosteronism. There have been studies suggesting there may be a link between incidence of hyperkalemia and the use of washed or unwashed blood products and length of RBC storage [51].

Abbreviations

ICU	Intensive Care Unit
RAAS	Renin Angiotensin Aldosterone System
mEQ/L	milli-equivalent per liter
mMol/L	milli-mole per liter
V2 receptors	Vasopresin 2 receptors
NaCl	Sodium Chloride
Lab	Laboratory
ADH	Anti-Diuretic Hormone

Mosmol	Milli-osmols
EABV	effective arterial blood volume
SIADH	syndrome of inappropriate anti-diuretic hormone
Mcg	microgram
SubQ	subcutaneous
D5W	5% dextrose solution in water
MRI	magnetic resonance imaging
DWI	diffusion weighted imaging
EKG	electrocardiogram
AKI	acute kidney injury
ESRD	End-stage renal disease
DKA	diabetic ketoacidosis
IV	intravenous
Mg	milligram
Dl	deciliter
Vit D	Vitamin D
TPN	total parenteral nutrition
PTH	parathyroid hormone
GI	gastrointestinal
ATN	acute tubular necrosis
CRRT	continuous renal replacement therapy
PO	per-oral
MTP	massive transfusion protocol

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