

Hyperchloremia in Critically Ill Patients in ICU: Review Article

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ABSTRACT

Background: Chloride (Cl) is required for the regulation of blood pressure, renal function, gastrointestinal homeostasis and decarboxylation/gas transport. "Dyschloremia" or levels of serum Cl beyond the normal range, is a frequent occurrence in intensive care units and seems to be mostly caused by iatrogenic procedures (i.e. intravenous infusion of fluids rich in Cl). Hypochloremia and hyperchloremia seem to be related to high risk of death in specified intensive care unit (ICU) groups, although the data is inconclusive. Hyperchloremia may be associated with higher hemodynamic unstable changes and need for vasopressors, in addition to hyperchloremic metabolic acidosis (e.g., following major surgeries). Nonetheless, the direct or indirect mediation of these effects is still uncertain. Additionally, new research suggests that individuals with advanced hyperchloremia have a higher risk of acute renal damage and require renal replacement treatment. **Objective:** The purpose of this study was to describe significant chloride-related outcomes in critical illness and to evaluate their relevance for everyday clinical practice and therapeutic alternatives. **Conclusion:** One may conclude that the concern about understanding the impact of chloride disorders on negative outcomes is rising; there seems to be a link between chloride disorders and negative outcomes, particularly death, in the ICU setting; one could theorize the need to rationalize the use of solutions with electrolyte components separate from the physiological solutions; and consider the presence or the development of hyperchloremia as a prognostic factor, without taking into consideration the severity of the critical patient.

Keywords: Hyperchloremia, Dyschloremia, Treatment of hyperchloremia.

INTRODUCTION

Hyperchloremia is common in critically sick patients, with evidence indicating that it may occur in between 25%–45% of ICU patients; nevertheless, it appears not to be mentioned in earlier studies or textbooks⁽¹⁾. Temporary hyperchloremia occurs in around 75% of ICU patients within the initial 24 hours of their hospitalization. Despite its relatively high occurrence in critically sick patients, insufficient data on the outcome of systemic chloride levels are available. According to current evidence, higher illness severity is often related with aberrant chloride levels⁽²⁾.

Definition of "dyschloremia":

- **Hypochloremia** is often described as serum Cl concentrations of less than 96–101 mmol/l.
- Typically, **hyperchloremia** is characterized as serum Cl concentrations more than 106–111 mmol/l.

The definition differs by laboratory. Chloride levels are inextricably linked to the body's water contact and are very vulnerable to plasma changes in contraction or dilution⁽³⁾.

Causes of hyperchloremia:

- **Pseudohyperchloremia:** When procedures requiring sample dilution are utilized, large volumes of serum solids (proteins or lipids) are produced. Bromide or iodide poisoning⁽⁴⁾.
- **Excessive administration of chloride:** Consuming a large amount of 0.9% (isotonic) NaCl solution.

- **Hypertonic saline administration:** Drowning in saltwater.
- **Losses of net water:** Perspiration (excessive sweating), fever, diabetes insipidus, and inadequate water intake.
- **Water loss due to an excess of electrolytes:** Some types of diarrheas, osmotic diuresis, and some instances of post-obstructive diuresis.
- **Metabolic acidosis-associated hyperchloremia:** Some types of diarrheas, carbonic anhydrase inhibitors, acidosis of the renal tubules, intake of ammonium chloride (NH₄Cl), ureteral diversion (e.g., ileal bladder), consumption of lysine hydrochloride or arginine, some types of chronic renal disorders, and organic acidosis that results in rapid excretion of acid anion (e.g. toluene overdose).
- **Respiratory alkalosis**⁽⁵⁾.

Pathophysiology:

Hyperchloremic metabolic acidosis (HMA) is a clinical condition that occurs due to the loss of bicarbonate rather than the generation or retention of acid. Loss of bicarbonate happens in a number of mechanisms that result in HMA: renal causes, gastrointestinal (GI) causes, and exogenous reasons⁽⁶⁾.

• Gastrointestinal causes:

Pancreatic fistula, nasojejunal tube suctioning from the duodenum, severe diarrhea and prolonged laxative usage all result in GI bicarbonate loss. Normally, some bicarbonate is released into the



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intestinal lumen to neutralize the acidic environment created by stomach emptying. The bicarbonate is reabsorbed in the form of bile across the length of the small intestines. However, in diseases associated with profuse watery diarrhea, bicarbonate is lost via the stool as a result of the increased intestinal motility⁽⁷⁾. This results in increased bicarbonate production from the intestinal mucosa and pancreas, which results in total acidifying of the blood. Similarly, pancreatic fistula results in an abnormal amount of bicarbonate being secreted into the intestines by the pancreas⁽⁸⁾.

This extra bicarbonate is eventually excreted in the feces. Nasojejunal suctioning eliminates bicarbonate from the duodenum or jejunal space through direct suctioning of the luminal contents. The common denominator across these illnesses is bicarbonate loss from the gastrointestinal regions, which results in an acidotic condition in the blood through unopposed hydrogen in the buffering system, as described before⁽⁸⁾.

- **Renal causes:**

Hyperchloremic acidosis in the kidneys may be caused by distal (DRTA), proximal renal tubular acidosis (PRTA), or use of carbonic anhydrase inhibitors on a long-term basis⁽⁹⁾.

DRTA (type 1) is a condition in which the distal nephron fails to produce hydrogen into the urine in an acceptable amount. This leads in alkaline urine and blood acidity. Inability to secrete hydrogen corresponds directly with NH_4 levels in urine and may be inferred by a positive urine anion gap, as shown before⁽²⁾.

PRTA (type 2) is a condition in which bicarbonate is not properly reabsorbed. This results in loss of bicarbonate in the urine. As a consequence, the blood becomes acidic and the urine becomes alkaline. Hypokalemia is related with both kinds of renal tubular acidosis (RTA)⁽⁶⁾.

Carbonic anhydrase inhibitors such as acetazolamide cause a medically induced type 2 PRTA by reducing bicarbonate reabsorption in the proximal nephron⁽⁷⁾.

Evaluation:

As with any disease, the most critical first step in assessment is a complete history and physical examination. Hyperchloremic acidosis is readily obvious as a result of gastrointestinal bicarbonate loss or pharmaceutical use⁽¹⁰⁾.

A complete blood count is necessary to ascertain the infectious cause of an elevated count of white blood cells and fluid body state as determined by hematocrit and hemoglobin levels. A comprehensive metabolic panel is necessary, with a focus on sodium (Na), potassium (K), and chloride (Cl) values, since they may be used to calculate the anion gap value⁽⁶⁾.

Arterial blood gas assessment is required to evaluate the pH state and to rule out metabolic acidosis. As noted before, the urinary anion gap is a critical parameter in hyperchloremic acidosis for determining the urine ammonium excretion status^(11, 12).

- **Exogenous causes:**

Numerous extrinsic triggers of hyperchloremic acidosis are plausible hypotheses. When NH_4Cl and hydrochloric acid are consumed, they react with bicarbonate in an effort to bring the pH level back to normal. However, this depletes the body's bicarbonate supplies, resulting in an acidotic state. Resuscitation with a high volume of 0.9 percent normal saline resulted in an overflow of Cl ions into the circulation⁽¹³⁾.

Impact of hyperchloremia in critical illness:

Normal saline (0.9% sodium chloride solution) is the most frequently used Cl-rich solution in clinical practice, particularly in critically sick patients and before operations. Opposing to its name, 0.9% saline is not a neutral or normal solution in actuality. When compared to plasma, it contains a supraphysiological level of Cl (154 vs. 100 meq/L, respectively)⁽⁵⁾.

Frequent administration of a solution with a high concentration of Cl results in HMA in critically ill individuals, which has a number of adverse consequences, particularly in severely septic patients and patients with septic shock⁽³⁾.

Hyperchloremia has been linked to acute renal damage in intensive care unit patients, and in cases of the presence of severe acidosis reduced inotrope effectiveness and cardiovascular dysfunction may occur. All of these adverse consequences of hyperchloremia contribute to an increase in mortality⁽¹⁰⁾.

During the salvage phase of septic shock, patients in critical condition are often given 0.9% saline, putting them at risk of HMA and other adverse consequences of hyperchloremia in the post-resuscitation phase⁽⁶⁾.

Observational studies examining the link between hyperchloremia and hospital mortality have produced inconsistent findings and involved a limited number of septic patients admitted to the intensive care unit⁽⁷⁾.

Interestingly, multiple investigations found that increasing serum Cl levels alone, unrelated to intravenous fluid, were linked with an increased risk of acute kidney injury (AKI). Concerning Cl levels, research indicates that only minimum and/or maximal Cl levels during ICU stay, but not ICU entrance levels, are related with an elevated likelihood of AKI. In one investigation, increasing Cl serum levels by 10 mmol/l resulted in an incidence rate of 7.39 % for the development of AKI. However, the number of studies examining Cl levels in the absence of intravenous fluids is relatively limited⁽⁹⁾.

Effect on clinical outcomes of critically ill patients:

- **Hyperchloremic metabolic acidosis**

HMA occurs as a consequence of large amounts of Cl-rich fluids being infused into critically unwell individuals. It develops dose-dependently and independently of the rate of infusion. Notably, HMA may impact healthy volunteers when a total volume of

2000 ml of Cl-rich infusate is used as well as ICU patients with acute kidney injury (AKI), but also⁽¹⁴⁾.

HMA may result in vasodilation, altered neurotransmitter function, reduced cardiac responsiveness, and other cellular alterations, as well as decreased endogenous catecholamine production.⁽⁶⁾

Cl-rich infusates have been linked to the onset of transient HMA. However, the latter's importance and impact on clinical outcomes such as the incidence of renal failure or death remain unknown⁽¹⁵⁾.

- **Renal function:**

Over 30 years ago, the effects of hyperchloremia on renal function were initially examined. There is some evidence from animal and human studies that suggests that Cl infusion reduces renal blood flow and renal cortical perfusion. However, a newly released trial contradicts these conclusions.⁽¹⁶⁾

Clinical trials, like animal tests, revealed inconsistent findings on patient-centered clinical outcomes (e.g. the requirement for renal replacement therapy (RRT) in intensive care unit (ICU) patients. While some clinical studies failed to detect changes in serum creatinine or acute kidney injury (AKI) rates in mixed intensive care unit (ICU) populations, cardiac surgery, or sepsis. Other publications indicate increased AKI incidence and the requirement for renal replacement therapy (RRT)⁽¹⁷⁾. However, a sensitivity analysis of one of these studies revealed that other undiscovered factors also increased the frequency of AKI and the requirement for renal replacement treatment, indicating that the problem is far from resolved⁽⁶⁾.

This is further substantiated by a recent retrospective investigation comparing hypertonic (3%) to normal saline in patients having emergency laparotomy, which found no difference in renal outcomes between the groups, despite the fact that the hypertonic saline group had much higher Cl levels⁽¹⁸⁾. Additionally, technique, nomenclature, total volume administered, and RRT triggers varied significantly across experiments. In general, experiments using a smaller total quantity of Cl infusion (i.e., 1–2 L/24 h) seem to have shown no effect on AKI rates⁽¹⁹⁾. Whereas studies with greater infusion rates shown an increased incidence of AKI and the requirement for RRT, indicating a dose-dependent impact. Despite the significant variability of the current evidence, a recent meta-analysis of randomized and non-randomized studies indicated that the use of Cl-rich fluids is related with an increased risk of AKI⁽²⁰⁾. Interestingly, some investigations found that increasing serum Cl levels alone, unrelated to intravenous fluid, were linked with an increased risk of AKI. Concerning Cl levels, research indicates that only minimum and/or maximal Cl levels during ICU stay, but not ICU entrance levels, are related with an elevated likelihood of AKI. In one investigation, increasing Cl serum levels by 10 mmol/l resulted in an incidence rate of 7.39 % for the development of AKI. However, the

number of studies examining Cl levels in the absence of IV fluids is still rather small⁽¹⁷⁾.

To summarize, despite the numerous research addressing the development of AKI and the necessity of RRT in patients receiving Cl-rich infusates, the issue is far from settled due to significant diversity in the available information.⁽¹⁶⁾

- **Cardiovascular function:**

Hemodynamic instability may occur as a result of Cl-rich infusions. **Kim and colleagues** originally documented the hemodynamic effects of Cl-rich fluids in a mouse sepsis model⁽²¹⁾.

Hypochloremia and the resulting metabolic acidosis resulted in a drop in arterial pressure. Additional investigations validated this effect, demonstrating lower mean arterial blood pressures and cardiac index in rats suffering from abdominal sepsis. Patients receiving Cl-rich infusions demonstrated a volume-dependent increase in vasopressor need in critically sick individuals⁽²²⁾. A randomized controlled double-blind research was conducted and demonstrated that the impact is not only volume-dependent, but also time-dependent in patients following major abdominal surgery when normal saline is compared to an acetate-buffered infusion solution. The mechanisms behind this impact remain a mystery. Additional studies comparing the cardiovascular stability of various infusion solutes are undoubtedly required before concluding⁽²³⁾.

Cl's effect on the cardiovascular system might be significant for doctors for a variety of reasons: To begin, Cl loading may increase catecholamine requirements in severely unwell individuals. Second, Cl levels may impact heart function in a "U-shaped" response curve, with hypo- and hyperchloremia being deleterious to cardiovascular stability and function, respectively⁽²¹⁾. Third, Cl-"loading" may have a dose-dependent influence on hemodynamic stability. Fourth, it has been shown in preclinical animals that simple hyperchloremia may result in elevated blood pressure. Only concurrent hyperchloremia and metabolic acidosis, on the other hand, leads in a reduction in systemic pressures. Thus, it is probable that acidosis, rather than hyperchloremia per se, is responsible for the observed deleterious cardiovascular consequences⁽²³⁾.

- **Inflammation and coagulation:**

Following Cl-rich infusions, systemic levels of inflammatory mediators were raised in various animal models. This was reported in both sepsis and trauma experimental paradigms. This is still debatable in humans, since the effects of Cl-rich infusions on inflammatory markers may be ascribed to sodium rather than to Cl. This, nevertheless, needs more elucidation⁽³⁾.

Cl-rich infusions have been related with an increased requirement for blood products in preclinical studies. Additionally, there is little evidence that

hyperchloremia may have an effect on plasmatic coagulation cascades and/or platelet function⁽³⁾.

In humans, multiple studies and a recent meta-analysis indicated that patients receiving Cl-rich infusions need greater blood product delivery. However, the impact of acidosis in this situation remains unknown⁽²⁴⁾.

Immunity:

For a number of reasons, comprehending the impact of acid–base balance on the inflammatory reaction is critical for clinical practice. To begin, present gaps in our knowledge of acidosis's impact on a broad number of cellular processes have resulted in dispute about how patients are handled in a variety of clinical contexts. While the majority of doctors disregard the effects of exogenous Cl⁻ on pH, many will treat modest instances of acidemia. Additionally, all kinds of metabolic acidosis tend to be related with an increased duration of stay in the hospital and critical care unit. Because metabolic acidosis is often caused and managed by doctors, it is critical to understand the physiologic effects of changed pH⁽²⁵⁾.

Second, our capability to regulate cellular processes through acid–base balance will be contingent upon a better knowledge of the link between pH and the manufacture and release of inflammatory chemicals. Researchers are still investigating ways to control the inflammatory response as a main treatment for sepsis and associated diseases. These efforts have been directed not just at decreasing pro-inflammatory mediators in order to prevent tissue harm, but also at enhancing the inflammatory response to infection⁽²⁴⁾.

This attention extends to other sectors as well, such as autoimmune disorders and cancer treatment. For example, reduced pH in human lymphokine-activated killer cells, human IL-2-stimulated lymphocytes, and mouse natural killer cells has been associated with decreased lymphocyte activity. Although the processes behind these effects are unclear, they most likely do not require energy substrate depletion⁽²¹⁾.

Third, manipulating pH as initial means of manipulating the inflammatory response is not feasible or desirable, understanding the way pH influences this response is necessary for interpreting data from immune-modulation studies; avoiding unintended immune-modulation in clinical and laboratory settings; and exploring the capacity of pH to improve the effectiveness of existing treatments. Finally, gaining a better knowledge of how pH is involved in the control of inflammation through intracellular signaling pathways or other mechanisms may eventually result in the development of new immunomodulatory techniques⁽²²⁾.

Treatment / Management:

Patients with hyperchloremic acidosis may not always have adverse symptoms as a result of the hyperchloremia. However, acidosis may have a variety of negative health consequences. Common problems include a lack of energy, headache, nausea, and

vomiting. However, when the acidosis progresses, stupor, coma, myocardial insufficiency, or cardiac arrest may develop. It is predicted that the respiratory rate would rise as the body strives to compensate by lowering CO₂; but, in chronic illness, this may result in muscular exhaustion and respiratory failure⁽²⁶⁾.

In every episode of hyperchloremic acidosis, the primary objective of treatment is to identify and cure the pathological event that precipitated the condition. If these individuals develop respiratory exhaustion and failure, they will need intubation and mechanical ventilation⁽²⁷⁾.

Hyperventilation under ventilator control may assist in reducing the acid load. When gastrointestinal reasons are suspected, it is critical to deliver intravenous (IV) saline to maintain fluid load, since patients may rapidly become dehydrated as a result of diarrhea or bowel suctioning⁽²⁸⁾. Furthermore, electrolytes must be checked and replaced as necessary. The K level is very critical. Until the underlying pathology is corrected, the acidosis is regulated by adding bicarbonate to saline⁽²⁹⁾.

In cases of RTA, high doses of bicarbonate may be required. If fluid excess is a problem, diuretics with added potassium may be provided. If the acidosis persists after treatment, it may be required to use dialysis⁽²⁶⁾.

As is customary, several drugs are tested to cause hyperchloremic acidosis and need to be stopped on taken cautiously. It is well established that cholestyramine, magnesium sulfate, and calcium chloride usage depletes gastrointestinal bicarbonate. Lead, streptozotocin, arginine, mercury, gentamicin, valproic acid and obsolete tetracycline ifosfamide use are all related with PRTA. Toluene, amphotericin B, lithium and nonsteroidal anti-inflammatory medications usage are all related with DRTA⁽²⁷⁾.

Treatment of hyperchloremia⁽³⁰⁾:

The following medications may help to decrease blood Cl levels and metabolic alkalosis⁽³¹⁾:

1. Carbonic anhydrase blockers.
2. Diuretics and corticosteroids (short-term treatments).
3. Arginine hydrochloride.
4. NH₄Cl.
5. Lysine Cl.
6. KCl.

Hyperchloremic metabolic acidosis:

(acidosis of the non-anion gap: unmeasured anions decreased, Cl- increased)⁽³⁰⁾.

Treatment:

Hydration solutions incorporating sodium bicarbonate, sodium acetate, sodium citrate, or sodium phosphate in place of chloride. Bicarbonate replacement of 1-2 meq/kg/day is recommended to achieve a serum HCO₃ concentration of 22-24 meq/L. Serum K levels are also often low in distal RTA. Addition of potassium citrate as required⁽³¹⁾.

RTA (Type 2, 'Proximal') significantly decreased proximal bicarbonate reabsorption, leading to a decrease in serum bicarbonate concentration. Increasing filtered bicarbonate load beyond the decreased capacity for resorption, result in metabolic acidosis. Fanconi Syndrome is one example; impaired proximal tubular function resulting in phosphaturia, glycosuria, and proteinuria⁽³¹⁾.

Treatment of hypochloremia:

1) Treatment of the Causes⁽³²⁾:

Diarrhea, vomiting, diuretics, gastrointestinal suction, water intoxication, syndrome of inappropriate antidiuretic hormone secretion, (SIADH), adrenal insufficiency, excessive sweating, drugs (ex: bicarbonate, laxatives, corticosteroids), and hyperaldosteronism.

Basic metabolic panel, comprising glucose and creatinine; hypochloremia may arise as a consequence of substantial volume loss and dehydration, accompanied by hypokalemia, hyponatremia, and metabolic alkalosis.

2) Fluid therapy⁽³³⁾

To restore intravascular volume, resuscitation with a Cl-rich isotonic fluid, such as 0.9 percent normal saline, is necessary. Following that, fluid management should be maintained with careful treatment of concomitant hypokalemia. However, when Cl levels are restored, serum bicarbonate values revert to normal and serum K concentrations increase. Periodic examinations of the basic metabolic panel may be necessary.

3) Eating Cl-rich foods⁽³⁴⁾:

Normally, Cl is eaten in the form of salt (60 percent Cl) or salt-containing meals. Additional meals with a somewhat high chloride concentration include the following: bacon, blue cheese, bread, butter, olives in brine, prawns, salami and stock cubes. Hypochloremia is described as a drop in Cl level below 95-100 mEq/L.

The following hereditary disorders are related with an unusually low quantity of chloride:

1) Bartter's syndrome⁽³⁵⁾:

Bartter's syndrome is an extremely uncommon genetic abnormality of the kidney cells in the section of the kidney responsible for electrolyte reabsorption (loop of Henle). It is defined by the following: Low blood Cl levels, K wasting, increased renin levels in the blood, metabolic alkalosis (high blood pH), normal blood pressure, increased secretion of aldosterone, repetitive need to drink and urinate, and high urine prostaglandin levels.

Mutations in the $\text{Na}^+/\text{K}^+/\text{2Cl}^-$ cotransporter 2 (NKCC2) cause this syndrome. Also, it may be caused by the following associated proteins: ClC-Kb (chloride voltage gated channel Kb) a protein that transports Cl out of cells, ROMK (renal outer medullary K channel) a protein that transports K out of cells, and CaSR

(a calcium levels-detecting protein that acts as a trigger to stimulate transporters of electrolyte)⁽³⁵⁾.

2) Gitelman's syndrome⁽³⁵⁾:

Gitelman's syndrome is a genetic condition with symptoms similar to those of Bartter's (metabolic alkalosis with low K, low Cl, elevated renin, and elevated aldosterone levels in the blood), but caused by abnormalities in a different location of the kidney cells (distal convoluted tubule). The disorder is initiated by mutations in the Na^+/Cl^- cotransporter (NCCT).

3) Cystic tissue scarring⁽³⁴⁾:

Cystic tissue scarring is a genetic condition that manifests itself via the following symptoms:

Accumulation of mucus, excessive salt concentration in perspiration, airway damage, lung disorders that are often seen, failure of the pancreas, coughing often, diabetes development, failure of the kidneys, insufficient bone mineral density, disorders of blood clotting, difficulty of growth and weight increase (in children), and in terms of electrolyte balance, cystic tissue scarring results in decreased blood levels of Cl, sodium, and K and increased blood levels of bicarbonate⁽³³⁾.

4) Addison's disease⁽³⁵⁾:

Addison's disease is a rare inherited condition in which the glands above the kidneys malfunction and generate insufficient cortisol and aldosterone. The following are the primary signs of this disorder: appetite loss, general fatigue and exhaustion, craving for salt, weight loss, low blood pressure, darkening of skin areas, high blood levels of K, and low blood levels of sodium and Cl.

5) Congenital Cl diarrhea⁽³⁵⁾:

Congenital Cl diarrhea is a rare hereditary condition that manifests as watery diarrhea with a high Cl content. It results in dehydration, metabolic alkalosis, and low blood chloride, sodium, and potassium levels. The disorder is caused by a malfunction in the bowel's chloride and bicarbonate transporters.

7) Syndrome of inappropriate antidiuresis⁽³⁵⁾:

This condition is defined by decreased water excretion, continuous synthesis or activity of the antidiuretic hormone vasopressin, and low salt and chloride levels in the blood. The condition is caused by activating mutations in the vasopressin receptor AVPR2, which results in an abnormally high level of water buildup.

CONCLUSION

One may conclude that the concern about understanding the impact of chloride disorders on negative outcomes is rising. There seems to be a link between chloride disorders and negative outcomes, particularly death, in the ICU setting. One could theorize the need to rationalize the use of solutions with electrolyte components separate from the physiological solutions; and consider the presence or the development

of hyperchloremia as a prognostic factor, without taking into consideration the severity of the critical patient.

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