International Clinical and Medical Case Reports Journal
Review Article (ISSN: 2832-5788)

Chloride: The Forgotten Ion

Oscar Miguel Oliva Meza-Hernández[1*], Elizabeth Cárdenas Anaya[2], Norma Alejandra Márquez Sáinz[3], María Cristina Quevedo Villaseñor[4], Héctor Luis Guillermo Macías Villa[5], Cecilia Ramírez Angulo[6], Alma Paola Alonso Bringas[7]

[1]Pediatric Intensive Care Unit, ABC Medical Center Santa Fe, Mexico City, Mexico

[2]Pediatric Gastroenterology, ABC Medical Center Santa Fe, Mexico City, Mexico

[3]Neonatology, ABC Medical Center Santa Fe, Mexico City, Mexico

[4]Neonatology, ABC Medical Center Santa Fe, Mexico City, Mexico

[5]Pediatric Nephrology, ABC Medical Center Santa Fe, Mexico City, Mexico

[6]Pediatrics, ABC Medical Center Santa Fe, Mexico City, Mexico

[7]Pediatrics, ABC Medical Center Santa Fe, Mexico City, Mexico

Citation: *Oscar Miguel Oliva Meza-Hernández, Elizabeth Cárdenas Anaya, Norma Alejandra Márquez Sáinz, María Cristina Quevedo Villaseñor, Héctor Luis Guillermo Macías Villa, Cecilia Ramírez Angulo[6], Alma Paola Alonso Bringas. Chloride: The Forgotten Ion. Int Clinc Med Case Rep Jour. 2025;4(8):1-12.*

Received Date: 13 August 2025**; Accepted Date:** 15 August 2025**; Published Date:** 17 August 2025

[*]**Corresponding author:** Oscar Miguel Oliva Meza-Hernández, Pediatric Intensive Care Unit, ABC Medical Center Santa Fe, Mexico City, Mexico

ABSTRACT

Chloride (Cl-) is the most common anion in intracellular and extracellular fluid. It maintains acid-base balance, plasma oncotic pressure, osmolarity, the resting action potential, and carbon dioxide transport in erythrocytes. It keeps serum concentrations within a very narrow range through hormonal control by the renin-angiotensin-aldosterone system and cortisol. In practice, we have rarely asked ourselves how to calculate the Cl- when we prescribing intravenous solutions to a patient, but we must remember that even a minor change in the Cl- concentration is enough to produce not only a profound alteration of the acid-base balance and thus adverse effects in practically any organ system, as explained by the Stewart model through the strong ion difference (SID), where the smaller the difference between cations and anions [(Na+, K+, Ca+ and Mg+) - (Cl- and lactate)], the higher the concentration of hydrogen ions [H+] and therefore hyperchloremic metabolic acidosis. The measured use of chloride solutions should guide medical conduct at the time of their administration.

Keywords: Chloride; Hyperchloremia; Hyperchloremic metabolic acidosis

INTRODUCTION

Chloride (Cl^-) is the most common anion in both intra- and extracellular fluid. Its normal serum concentration ranges from 96 to 107 mEq/L. Despite its clinical relevance and its role in physiological, cellular, organic, systemic, and even signaling pathway processes, we rarely consider the actual requirement for this ion or the

potential impact of supraphysiological levels. Although chloride is a major component of 0.9% saline solution the most widely used intravenous fluid worldwide it remains the "forgotten ion." This review aims to highlight the importance of this anion and the deleterious systemic effects that may result from overlooking it.

DISCUSSION

Chloride (Cl^-) is the most common anion in both intra- and extracellular fluid. It plays a critical role in maintaining acid–base balance (Cl^- and bicarbonate exhibit an inverse relationship), plasma oncotic pressure, osmolarity, resting membrane potential, and carbon dioxide transport within red blood cells (RBCs). Normal serum chloride concentration (free and RBC-bound) ranges from 96 to 107 mEq/L, while the intracellular concentration is approximately 4 mEq/L.[1] Chloride constitutes 70% of all negatively charged atoms or groups in the body, and its role in physiological, cellular, systemic, and even signaling pathway processes is so important that, in recent years, debate has emerged regarding the safety of crystalloid solutions in terms of their chloride content.[2]

In clinical practice, we rarely question how to calculate chloride intake when prescribing intravenous fluids. Before dismissing such considerations by arguing that calculations are based on sodium levels, it is important to remember that even a minimal change in chloride concentration can cause profound alterations in acid–base balance, as explained by Stewart's physicochemical approach through the strong ion difference (SID) model.[3] Beyond acid–base changes, hyperchloremia can induce pro-inflammatory effects, reduce mean arterial pressure, and inhibit erythropoiesis. Accounting for two-thirds of plasma's negative charges positions chloride as a fundamental ion.[4]

According to Stewart's model, the three factors determining acid–base status (pH) are:

a) Strong ion difference (SID)

b) Partial pressure of carbon dioxide (pCO_2)

c) Concentration of weak acids (Atot)

Strong ions are those completely dissociated in plasma. Therefore, SID is calculated as the total concentration of dissociated plasma cations (Na^+, K^+, Ca^{2+}, Mg^{2+}) minus dissociated plasma anions (Cl^- and lactate). The normal SID is approximately 40 mEq/L.[5] In this model, hydrogen ion concentration [H^+] results from water dissociation ($H_2O \rightleftharpoons H^+ + OH^-$) in response to changes in SID. Nearly all biological solutions contain water, which provides an inexhaustible source of [H^+] when OH^- ions dissociate in response to SID variations.

When anion concentration (particularly Cl^-) increases and the difference from Na^+ decreases, greater water dissociation occurs, releasing more [H^+] and leading to acidosis. Conversely, when the Na^+–Cl^- gap widens, OH^- concentrations rise, producing alkalosis. Thus, [H^+] concentration reflects the effects—rather than the primary causes of acid base imbalance.[6]

To achieve acid–base homeostasis (pH 7.35–7.45 and SID 40 mEq/L; Figure 1), Stewart's model applies two principles: the law of electroneutrality and the principle of conservation of mass. Under these principles, SID, pCO_2, and Atot together determine $[H^+]$ concentration.[7]

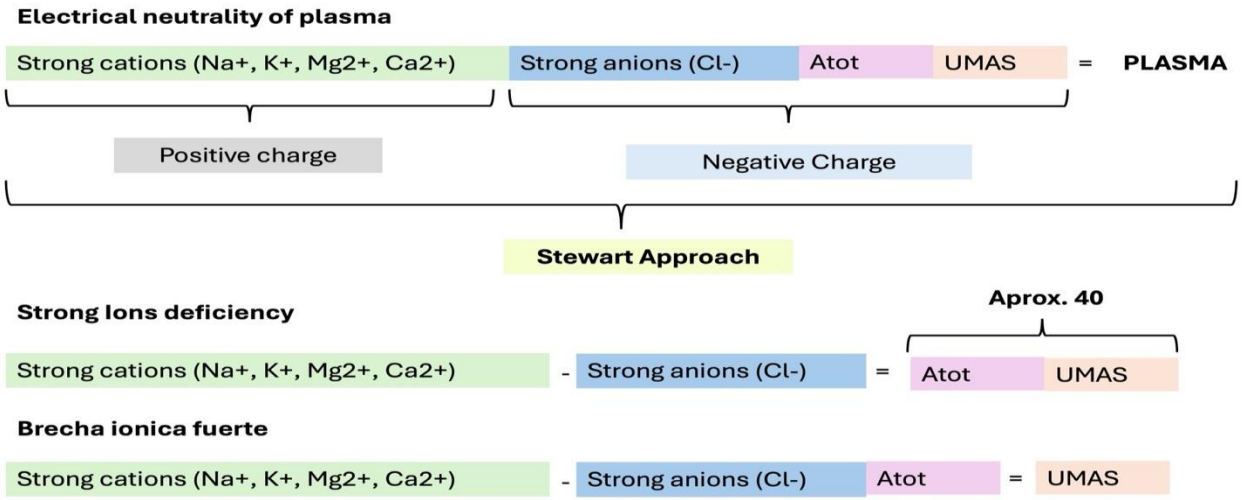

Figure 1: Stewart Approach

While sodium often receives greater clinical attention, chloride is equally indispensable for maintaining electroneutrality in body fluids. Under physiological conditions, Na^+ and Cl^- remain in balance to preserve electroneutrality. However, when hyperchloremia occurs without a proportional increase in sodium, normal anion gap metabolic acidosis develops due to a fall in serum bicarbonate (HCO_3^-).

Chloride levels may rise due to administration of large volumes of 0.9% saline (especially during fluid resuscitation), renal failure (impaired Cl^- excretion), diabetic ketoacidosis,[8] net water loss (increased proximal tubular absorption and reduced distal delivery, which enhances chloride concentration capacity—seen in diarrhea, renal tubular acidosis, carbonic anhydrase inhibitor use, or lysine/arginine administration), or even osmotic diuresis (Figure 2).

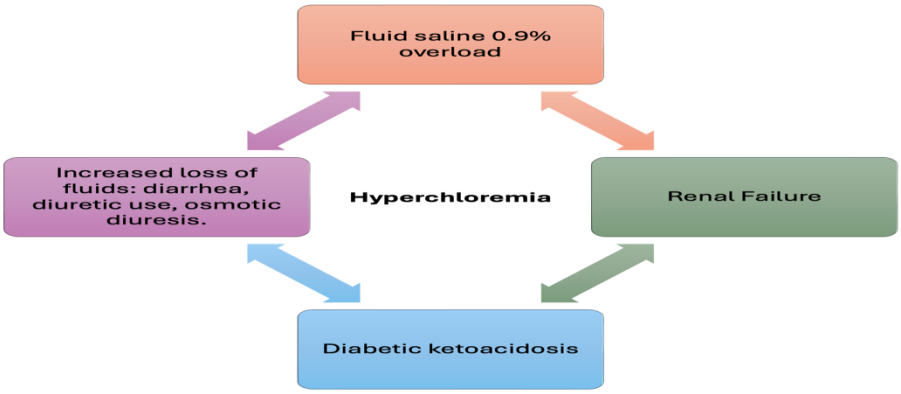

Figure 2: Hyperchloremia cause

Once a patient receives a large volume of 0.9% sodium chloride (NaCl) solution, serum chloride levels may take up to two days to return to normal. This slow excretory response is due to chloride's own effect on renal blood flow, which subsequently decreases the glomerular filtration rate (GFR). With isotonic saline administration, bicarbonate (HCO_3^-) concentration may also decrease as chloride rises.[9] This occurs because, in order to maintain the principle of electroneutrality, an increase in one anion must be accompanied by a decrease in another.

In routine clinical practice, fluid calculations usually account for sodium, potassium, calcium, magnesium, and even phosphorus. Chloride—most commonly administered in the form of 0.9% sodium chloride—is generally given implicitly, and we rarely ask the following questions: What is the chloride requirement in mEq per kilogram? Is 0.9% sodium chloride truly physiological and harmless? Could 0.9% sodium chloride alter the strong ion difference (SID)?

Remarkably, Turley and colleagues reported in a 2007 Critical Care article that only 13.8% of medical personnel knew the chloride concentration of 0.9% saline, despite it being the first-choice resuscitation fluid.[10] Bringing chloride into consideration when administering chloride-containing solutions may become easier if we bear in mind not only its potential side effects, but also the fact that chloride channels are present in virtually all plasma cell membranes and intracellular organelles, where they regulate cell volume, ionic homeostasis, electrical excitability, and transepithelial transport. In addition, chloride channels in intracellular organelles regulate organelle pH.[11]

Addressing the earlier questions, the daily chloride requirement is approximately 5 mEq/kg/day and is usually met through sodium chloride and potassium chloride administration.[12] However, increasing attention has been paid to the fact that 0.9% saline can cause hyperchloremic metabolic acidosis (HMA). Relatively small volumes of NaCl (30 mL/kg/h) can induce metabolic acidosis secondary to hyperchloremia, as described by Stewart's model.[13] The most frequent preventable cause of HMA is administration of fluids with supraphysiological chloride concentrations, such as 0.9% saline, which contains 154 mmol/L of chloride (about 1.5 times the plasma level, or 40–50% higher), exceeding the normal range of 96–107 mEq/L.

There is ongoing controversy over whether HMA induced by 0.9% saline is benign; however, this seems unlikely given the moderate decrease in pH. A systematic review published in 2025 concluded that the consistent finding across studies is the association between HMA and 0.9% saline administration, and that the presumed safety of hyperchloremic metabolic acidosis has not been demonstrated. The review also concluded that a slow replacement strategy is safer than rapid infusions, and that using balanced crystalloids such as lactated Ringer's or Plasma-Lyte may be preferable.[14]

The link between rapid 0.9% saline infusion and HMA is due to SID reduction caused by a sharp rise in chloride concentration, as well as excessive renal bicarbonate loss. Historically, acidosis has been considered the result of poor organ perfusion and myocardial dysfunction, often prompting the administration of 0.9% saline boluses

an intervention that may actually worsen acidosis. Thus, the main adverse effect of saline-induced HMA may be the very measure taken to correct the underlying abnormality.

Moreover, hyperchloremia increases renal eicosanoid release, causing vasoconstriction and a reduction in GFR. Kellum and Gunnerson also found that HMA has more deleterious effects due to its specific type (hyperchloremic) than from the degree of acidosis itself, as demonstrated by their description of a pro-inflammatory macrophage-like cell response induced by HMA.[15] This is particularly striking, as it suggests that chloride per se induces greater harm than the pH decrease itself.

This may be because the true physiological significance of chloride has been only marginally appreciated. Lesser-known physiological functions of chloride include regulation of enzymatic activity, gene expression, ion channels, ion transporters, ion pumps, ionic microenvironment, neurite elongation (dendrites or axons), cell death, autophagy, cell volume, cell proliferation, ciliary motion, epithelial sodium (Na^+) transport, Na^+/K^+ pump activity, and cytosolic regulation of intracellular signaling. This last function is likely among the most important in terms of the deleterious effects caused by dyschloremia, since alterations in cytosolic chloride concentrations can disrupt both intracellular signaling and biological functions. Therefore, chloride's role clearly extends beyond maintaining electroneutrality.[16]

Severe hyperchloremia (>110 mEq/L) is associated with high mortality due to disruption of electroneutrality. This is the result of an initial SID decrease, which lowers bicarbonate concentrations and increases free hydrogen ion (H^+) levels, triggering acidosis.[2,17] The following section describes chloride's effects on different organ systems (Figure 3).

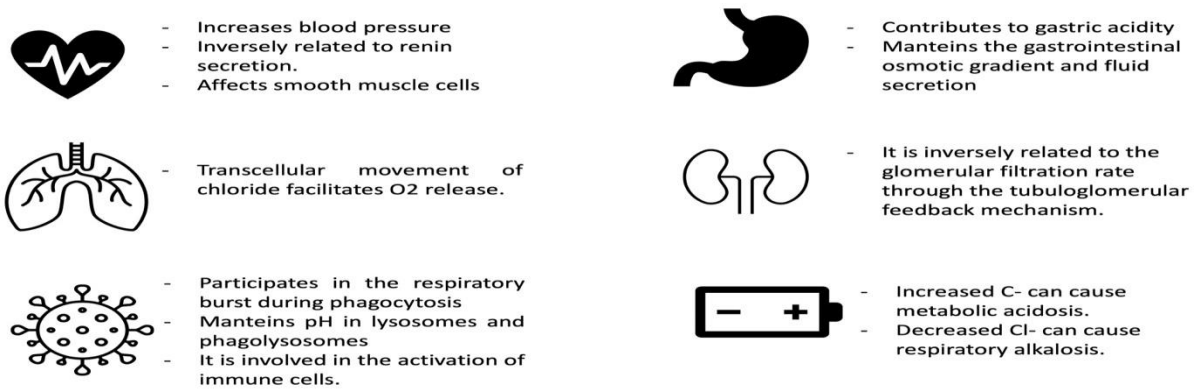

Figure 3: Chloride effects in the organism

Effects on the Renal System

At the renal level, hyperchloremia can increase interstitial and intraglomerular mesangial chloride concentrations, leading to afferent arteriole vasoconstriction. This occurs via the tubuloglomerular feedback mechanism triggered by chloride detection at the macula densa, which induces afferent arteriole vasoconstriction and reduces the glomerular filtration rate (GFR).[18]

In vitro evidence suggests that mesangial cell chloride permeability increases through activation of calcium-activated chloride channels, resulting in membrane depolarization and cellular contraction in response to ATP, angiotensin II, and vasopressin. Conversely, mesangial cells produce prostaglandin E_2 in response to low extracellular chloride, which reduces angiotensin II- and vasopressin-mediated contractility. Furthermore, low extracellular chloride decreases vasopressor responses mediated by endothelin-1 and vasopressin.

Therefore, changes in plasma or mesangial chloride concentration modulate the chloride gradient across the cell membrane, influencing the activity of mesangial cell and afferent arteriole smooth muscle chloride channels, and triggering contraction.[19] This was described by Suetrong et al., who found that, in septic shock patients, a rapid increase in chloride concentration >5 mmol/L was associated with the development of acute kidney injury (AKI), even in patients without hyperchloremia. This suggests that an abrupt change in chloride concentration may be more important than the absolute chloride value an alarming observation given that in most clinical volume resuscitation scenarios, 0.9% saline is administered. This not only alters the strong ion difference (SID) but also dilutes bicarbonate, producing dilutional acidosis, as demonstrated by randomized trials in which just two hours of 0.9% saline infusion reduced bicarbonate by 1–2 mmol/L.

A retrospective observational study of 19,707 patients showed that the risk of severe AKI (AKI > stage 2) increased 1.06-fold for every 1 mmol/L rise in chloride among critically ill patients. Interestingly, the study also found that for every 1 mmol/L negative fluctuation in chloride, the risk of AKI increased 1.04-fold.[20] This suggests that dyschloremia in general may contribute to AKI.

Moreover, greater interstitial fluid retention (interstitial edema) has been observed with 0.9% saline compared to balanced crystalloids, with this retention associated with reduced urine output. Small increases in organ volume within relatively noncompliant capsules can lead to intracapsular hypertension, compromising tissue perfusion, microvascular blood flow, and ultimately organ function.[18,21]

Huang et al. conducted a study comparing critically ill patients receiving chloride-liberal solutions (Cl^- 120–150 mmol/L) versus chloride-restricted solutions (Cl^- 98–122 mmol/L). Patients were followed for four months, with renal injury evaluated via KDIGO and RIFLE criteria, need for renal replacement therapy (RRT), and mortality. Results showed that the restricted group had a smaller Δ creatinine, lower AKI rates (less than half the risk in RIFLE and KDIGO stage 3), reduced need for RRT, and lower mortality.[22]

Although methodological differences, terminology, administered chloride volumes, and RRT initiation criteria vary across studies, the consensus is that lower chloride administration is not associated with increased AKI, while higher chloride exposure consistently correlates with greater AKI incidence and RRT need, suggesting a dose-dependent effect. Interestingly, elevated serum chloride levels per se, regardless of the type of fluid administered, are associated with increased AKI risk. However, perhaps most importantly for clinical decision-making, changes in chloride concentration during hospitalization—rather than admission values—were most strongly associated with higher AKI incidence.[23]

Hyperchloremia in Pediatrics

In pediatric patients, the scenario is similar. Celegen and colleagues, through multivariate logistic analysis, found that hyperchloremia at 48 hours after admission was an independent risk factor for mortality in pediatric patients aged 1 month to 18 years with major trauma admitted to intensive care. These patients had received solutions with NaCl concentrations ranging from >0.9% up to 3%. As in adult studies, non-survivors received greater fluid volumes, and chloride levels were similar at admission. Serum chloride levels >110 mEq/L were significantly more frequent among non-survivors.[24]

A recent study by Mitting et al., including 2,217 patients under 16 years of age (mean age 16.4 months), obtained arterial blood gases at admission and calculated GFR using the highest serum creatinine during hospitalization. The primary outcome was a decline in GFR during admission. After multivariate analysis, hyperchloremia (>110 mEq/L) at admission was associated with increased need for renal replacement therapy (RRT) and lower GFR. Sixty-three percent of patients had a GFR <75 mL/min at some point during hospitalization. After adjusting for clinically relevant confounders, admission chloride concentration was identified as an independent predictor of reduced GFR. These results were consistent with another study showing that increases in chloride during hospitalization were associated with higher rates of acute kidney injury (AKI) and mortality.[25]

The FEAST trial, conducted in 3,000 children with severe infection, concluded that boluses of 0.9% saline can cause hyperchloremic acidosis, as well as respiratory and neurological dysfunction.[26] Consequently, the Society of Critical Care Medicine recommended smaller fluid boluses in children with septic shock.[27]

For example, consider a pediatric patient admitted with bronchiolitis who receives 10 mL/h of 0.9% saline to maintain intravenous line patency. This patient would receive 36.96 mEq of chloride per day, meaning that any child weighing less than 7 kg would receive a daily chloride dose exceeding basal requirements. This calculation does not even take into account that most medications are diluted in 0.9% saline, and intravenous line flushes are also typically performed with the same solution. Alongside 5% dextrose (D5W) and mixed solutions (D5N5), 0.9% saline is among the most common diluents for initial and final antibiotic reconstitution, administered as boluses, slow infusions, intermittent doses, or continuous infusions.[28]

Currently, crystalloids are classified as balanced or unbalanced according to their composition, SID, or net cation–anion load. Balanced solutions have an SID close to that of plasma (40 mEq/L), whereas unbalanced solutions reduce SID. 0.9% saline is considered an unbalanced solution because its SID is zero. The most widely cited hypothesis for the harmful effects of unbalanced solutions involves the induction of metabolic acidosis and impairment of immune and renal systems. Hyperchloremic metabolic acidosis has been recognized in children as a consequence of fluid resuscitation.

Emrath et al. found that in pediatric patients with severe sepsis, the use of balanced solutions during the first 72 hours of fluid resuscitation was associated with improved survival, reduced AKI prevalence, and shorter vasoactive infusion duration compared to patients who received unbalanced solutions.[29] Conversely, Martínez et al. found no statistically significant difference in AKI incidence, infection, or mortality between children with

and without hyperchloremia. However, hyperchloremia was more frequent in children requiring extracorporeal renal replacement therapy.[30]

Overall, most studies report a strong association between hyperchloremia and altered function and metabolism in different organs, likely because hyperchloremia contributes to SID shortening, which in turn leads to increased hydrogen ion (H^+) release.

Effects of Hydrogen Ions

As a reminder, one of the determinants of plasma hydrogen ion concentration [H^+] is the strong ion difference (SID). As SID decreases, [H^+] increases and pH falls.[31] There are relatively narrow limits within which [H^+] is compatible with life, ranging from 16 to 160 nEq/L, corresponding to a pH range of 7.80 to 6.80. Under normal conditions, the [H^+] concentration in extracellular fluid is low (40 nEq/L).[32] An increase in [H^+] decreases pH.[33]

Separating the physiological effects of acidosis per se from those of the underlying pathology is nearly impossible; however, several organ-specific effects of acidosis are well described, such as decreased cardiac contractility and reduced responsiveness to inotropes. In isolated tissues, β-adrenergic responsiveness is reduced at pH values below 7.0.[34] Metabolic acidosis affects multiple organ systems, but its cardiovascular effects are the most critical—it decreases contractility, cardiac output (pH <7.20), and blood pressure. There is both inotropic and vasopressor resistance, and a predisposition to ventricular arrhythmias has been reported.

Even small changes in brain and cerebrospinal fluid pH can cause confusion and lethargy in patients with metabolic acidosis. During metabolic acidosis, interleukin production by macrophages is stimulated, while lymphocyte function is suppressed. Leukocyte chemotactic and bactericidal properties are reduced, increasing susceptibility to infection. Cellular energy production can also be compromised, as the activity of 6-phosphofructokinase a critical glycolytic enzyme is pH dependent.[35]

Thus, as previously discussed (Figure 3), hyperchloremia can impact multiple organ systems. It is likely for this reason that, under normal physiological conditions, serum chloride is maintained within a very narrow range through hormonal regulation by the renin angiotensin aldosterone system and cortisol. As a result of this strict homeostatic control, serum chloride concentration is not a sensitive marker of total body chloride status.[36] Since hyperchloremia can take up to two days to return to pre-treatment levels, even in healthy patients, and can result from the administration of large volumes of saline solution,[37] prudent use of chloride-containing solutions should guide medical decision-making at the time of administration.

Balanced Solutions

Historically, saline has been the most frequently used intravenous fluid. Balanced crystalloid solutions (such as lactated Ringer's, Hartmann's solution, and Plasma-Lyte) have sodium, potassium, and chloride concentrations closer to those of extracellular fluid and exert fewer adverse effects on acid–base balance.[38]

A systematic review and meta-analysis registered in the International Prospective Register of Systematic Reviews (PROSPERO) and including 11 studies plus 2 abstracts concluded that the estimated effect of balanced solutions versus 0.9% saline for fluid therapy in critically ill adults ranged between a 9% relative reduction and a 1% relative increase in 90-day mortality. This result remained consistent when applying alternative meta-analytic methods. In patients with sepsis, balanced solutions were associated with a 14% mortality reduction, whereas 0.9% saline was associated with a 1% increase. In severe traumatic brain injury, balanced solutions were associated with a 2% reduction in mortality. This represents the most updated evidence comparing balanced solutions and 0.9% saline.[39]

Another meta-analysis, including 18 studies, also evaluated mortality and renal injury in critically ill patients receiving balanced crystalloids versus 0.9% saline. The Newcastle–Ottawa Scale and the Cochrane Risk of Bias Tool were used to assess study quality. The authors concluded that balanced crystalloids reduce the risk of acute kidney injury (AKI) compared with saline, but found no difference in mortality. They acknowledged potential publication bias since both adult and pediatric patients were included.[40]

In patients with diabetic ketoacidosis (DKA), one study reported a shorter time to resolution of ketoacidosis in those who received balanced crystalloids compared with saline (13 hours vs. 16.9 hours, respectively). Additionally, insulin infusion could be discontinued earlier in the balanced group than in the saline group (9.8 hours vs. 13.4 hours). The most frequently used balanced solution was lactated Ringer's, followed by Plasma-Lyte.[41]

Undoubtedly, the intravenous fluid with a composition most similar to human plasma is the safest. The key difference between balanced and saline solutions is that balanced solutions contain anions other than chloride, preventing hyperchloremia. In fact, without even directly comparing the two types of solutions, it is evident that any deviation from normal physiological variables is associated with worse outcomes and saline induces hyperchloremia, as repeatedly mentioned.

There are few specific indications for repeated saline administration: metabolic alkalosis (for high chloride delivery), hyponatremia (for high sodium delivery), and severe traumatic brain injury (due to its normotonic composition). In the absence of these conditions, the use of saline should be restricted.[42]

Another advantage of balanced solutions is that they contain bicarbonate precursors, making them buffer solutions. Examples include sodium lactate (in Hartmann's solution) and acetate (in Plasma-Lyte), both of which are metabolized to bicarbonate, thus alkalinizing plasma. In healthy patients, lactated Ringer's does not raise serum lactate levels because it contains sodium lactate. Both lactated Ringer's and Plasma-Lyte contain potassium; however, they are safe in hyperkalemic patients. Studies in DKA, rhabdomyolysis, and post–kidney transplant patients have shown that serum potassium remains unchanged, with even higher potassium levels observed in some cases after saline administration.[43]

In a prospective pediatric study involving 186 patients with acute gastroenteritis, one group received 40 mL/kg of 0.9% saline while another received 40 mL/kg of Plasma-Lyte. The Plasma-Lyte group showed greater recovery of bicarbonate levels and lower chloride levels. No differences were found in Na^+ and K^+ concentrations.[44] Another pediatric review of patients with severe dehydration due to diarrhea, compiling five recent clinical trials, found that those receiving balanced solutions had higher pH and bicarbonate levels than those treated with saline. Balanced solutions reduced the risk of hypokalemia by 36% compared with saline. Indeed, the World Health Organization recommends lactated Ringer's for treating severe dehydration in children with diarrhea.[45]

Overall, the vast majority of studies both in children and adults indicate that balanced solutions are safe, effective, and the most reliable alternative for patients requiring large fluid volumes. Even in cases where lower fluid volumes are needed, balanced solutions remain a valid option to avoid hyperchloremic metabolic acidosis.

CONCLUSION

Chloride is the most abundant anion and plays a major role in maintaining acid–base balance. Administration of large volumes of solutions containing chloride at supraphysiological concentrations, such as 0.9% saline, can shorten the strong ion difference (SID) and increase plasma $[H^+]$. The resulting hyperchloremic metabolic acidosis can produce organ effects severe enough to independently increase the prevalence of acute kidney injury, as well as cardiovascular, immune, and neurological damage, ultimately impacting mortality. The use of such solutions is widespread in virtually all patients requiring care in emergency departments, hospital wards, operating rooms, and even in those receiving them solely to maintain intravenous line patency. Even small changes in chloride concentration can negatively affect acid–base balance; therefore, this electrolyte should always be considered when prescribing these types of solutions.

REFERENCES

1. Mittal K. Chloride in intensive care. Journal of Pediatric Critical Care 2020;7(2):95-96.
2. Astapenko D, Navratil P, Pouska J and Cerny V. Clinical physiology aspects on chloremia in fluid therapy: A systematic review.Perioperative Medicine 2020;9(40):1-8.
3. Burdett E, Roche A, Mythen M. Hyperchloremic acidosis: pathophysiology and clinical impact.Transfusion alternatives in transfusion medicine 2003;5(4):424-430.
4. Luglio M, De Carvalho Werther B, Tannuri U, Tannuri AC, Hideki Matsura R, et al. Effects of serum sodium and chloride levels in the outcome of critically ill pediatric patients in the post-operative period of liver transplantation. BMC Nephrology 2023;24(141):1-9.
5. Story D. Stewart acid-base:a simplified bedside approach. Anesth Analg. 2016;123(2):511-5.
6. WH George Y. From saline to more physiologic fluid. Easy way to understand Stewart's acid-base 2015;9.
7. Meza García M. Disturbios del estado ácido-básico en el paciente crítico. Acta Med Per. 2011;28(1):46-55.

8. Sagar N, Lohiya S. A comprehensive review of chloride management in critically ill patients. Cureus 2024;16(3):e55625.
9. Nagami G. Hyperchloremia: why and how. Nephrology. 2016;36(4):347-353.
10. Turley A, Bose B, Gedney J. Saline-induced hyperchloremic metabolic acidosis: an unrecognised phenomenon among medical staff?. Crit Care. 2007;11(Suppl 2):P314.
11. Planells-Cases R, Jentsch T. Chloride Channelopathies. Biochim Biophys Acta. 2009;1792(3):173-189.
12. Meyers R. Pediatric fluid and electrolyte therapy. J Pediatric pharmacol Ther. 2009;14(4):204-211.
13. Handy JM, Soni N. Physiological effects of hyperchloremia and acidosis. Br J Anaesth. 2008;101(2):141-50.
14. Abdulal I, Alanazi A, Alenezi A, Alshammari F, Alanazi G, Alanazi -N and cols. Saline-induced hyperchloremic metabolic acidosis: A systematic review. Journal of chemical health risks 2025;15(1): 333-340.
15. Eisenhut M. Causes and effects of hyperchloremic acidosis. Critical Care 2006;10(3):1-2.
16. Marunaka Y. Physiological roles of chloride ions in bodily and cellular functions. J Physiol Sci. 2023;73(1):31.
17. Sánchez-Díaz JS, Monares-Zepeda E, Meneses Olguín C, Rodríguez-Enríquez EA, García-Méndez RC, Peniche-Moguel KG and cols. Soluciones Balanceadas: Cloro el "nuevo villano".Med Crit 2017;31(3):152-158.
18. Suetrong B, Pisitsak C, Boyd J, Russell J, Walley K. Hyperchloremia and moderate increase in serum chloride are associated with acute kidney injury in severe sepsis and septic shock patients. Critical Care 2016;20(315):1-8.
19. Rein J, Coca S. "I don't get no respect". Am J Physiol Renal Physiol. 2018;316:587-605.
20. Oh T, Song IA, Jeon YT, Jo YH. Fluctuation in serum chloride and acute kidney injury among critically ill patients: A retrospective association study. J. Clin Med. 2019;8(447):1-14.
21. Lobo D, Awad S. Should chloride-rich crystalloids remain the mainstay of fluid resuscitation to prevent "pre-renal" acute kidney injury. Kidney Int. 2014;86(6):1096-105.
22. Huang L, Hu Y, Jia L, Pang M, Huang C, Zhao Z, Li L. Safety Analysis regarding acute kidney injuries for chloride-restrictive intravenous fluid administration against that of chloride-liberal for patients admitted in the medical intensive care unit: A non-randomised retrospective study. Int J Clin Pract. 2021;75:1-10.
23. Pfortmueller CA, Uehlinger D, von Haehling S, Schefold JC. Serum chloride levels in critical illness-the hidden story. Intensive Care Med Exp. 2018;6:10.
24. Celegen K, Celegen M. Effect of hyperchloremia on mortality of pediatric trauma patients: A retrospective cohort study. Sao Paulo Med J. 2024;142(4):1-6.
25. Mitting R, Ramnarayan P, Inwald D. Hyperchloremia on admission to pediatric intensive care in mechanically ventilated children is associated with impaired renal function. J Ped Intensive Care. 2021;12(1):18-23.
26. Maitland K, Kiguli S, Opoka R O. Mortality after fluid bolus in African children with severe infection. FEAST Trial Group. N Engl J Med. 2011; 364(26):2483–2495.

27. Weiss S L, Peters M J, Alhazzani W. Surviving Sepsis Campaign International Guidelines for the management of septic shock and sepsis-associated organ dysfunction in children. Pediatr Crit Care Med. 2020;21(02):e52–e106.
28. Sruthy KB, Unni J, Karunakaran P. Antimicrobial dilution for intravenous administration in children. Pediatric Infectous Disease 2022;4(2):47-61.
29. Emrath E, Fortenberry J, Travers C, McCracken C, Hebbar K. Resucitation with balanced fluids is associated with improved survival in pediatric severe sepsis. Crit Care Med. 2017;45:1177-1183.
30. Martínez RM, Viñas T, López-Herce J. Hipercloremia e hipernatremia en niños en estado crítico. Medicina Intensiva 2021;45(9):e59-e61.
31. Carrillo Esper R, Carrillo Córdova JR, Carrillo Córdova LD. Modelo fisicoquímico del equilibrio ácido-base. Conceptos actuales. Rev Fac Med UNAM 2008;51(4):156-158.
32. Fisiología del equilibrio ácido-base. Tomado de.
33. Malte H, Lykkeboe G. The Bohr/Haldane effect: a model-based uncovering of the full extent of its impact on O2 delivery to and CO2 removal from tissues. J Appl Physiol. 1985;125(3):916-922.
34. Handy JM, Soni N. Physiological effects of hyperchloremia and acidosis. Br J Anaesth. 2008;101(2):141-50.
35. Kraut J, Madias N. Metabolic acidosis: Pathophysiology, diagnosis and management. Nat. Rev. Nephrol. 2010;6:274-285.
36. Turck D, Castenmiller J, De Henauw S, Hirsh-Ernst K, Kearney J, Knutsen, H et al. Dietary reference values for chloride, EFSA Journal. 2019; 17(9):1-39.
37. Nagami G. Hyperchloremia: why and how. Nefrología. 2016;36(4):347-353.
38. Semler M, Kellum J. Balanced crystalloid solutions. Am J Respir Crit Care Med. 2019;199(8):952-960.
39. Hammond N, Zampieri F, Di Tanna GL, Garside T, Adigbli D, Cavalcanti A and cols. Ballanced crystalloids versus saline in critically ill adults- A systematic review with meta-analysis. NEJM Evid. 2022;1(2):EVIDoa2100010.
40. Wang P, Huang Y, Li J, Cao D, Chen B, Chen Z and cols. Balanced crystalloid solutions versus normal saline in intensive care units: A systematic review and meta-analysis. Int Urol Nephrol 2023;55(11):2829-2844.
41. Self W, Evans C, Jenkins C, Brown R, Casey J, Collins S, and cols. Clinical Effects of Balanced Crystalloids vs Saline in Adults with Diabetic Ketoacidosis. JAMA Network Open. 2020;3(11):1-13.
42. Vincent JL, De Backer D. Saline vs balanced solutions: are clinical trials comparing two crystalloid solutions really needed?. Crit Care. 2016;20(250):1-3.
43. Tomado de: https://epmonthly.com/article/the-fluid-debate-balanced-or-unbalanced
44. Fernandez Montes R, Alonso Álvarez MA, Fernández Miaja M, Vega López L, Álvarez Merino M y Garrido García E. Plasmalyte vs suero fisiológico para rehidratación rápida en gastroenteritis: estudio observacional prospectivo. Anales de Pediatría 2025;102:1-9.
45. Sierra JM. Líquidos balanceados en la rehidratación del niño deshidratado grave por diarrea. Evid Pediatr. 2023;19:37.