Exploration of Medicine

Open Exploration

Open Access Review

Issues on the horizon of normal saline intravenous infusion in critical care medicine

Jasen F. Saad[1,2], Fawzy A. Saad[1*]

[1]Department of Drug Discovery, Galaxies Pharmaceuticals, Juhkentali 8, 10132 Tallinn, Estonia
[2]Walker College of Business, Appalachian State University, Boone, NC 28608, USA

***Correspondence:** Fawzy A. Saad, Department of Drug Discovery, Galaxies Pharmaceuticals, Juhkentali 8, 10132 Tallinn, Estonia. fa_saad@yahoo.co.uk

Academic Editor: Yingyong Zhao, Northwest University, China
Received: November 11, 2025 **Accepted:** January 24, 2026 **Published:** June 11, 2026

Cite this article: Saad JF, Saad FA. Issues on the horizon of normal saline intravenous infusion in critical care medicine. Explor Med. 2026;7:1001411. https://doi.org/10.37349/emed.2026.1001411

Abstract

Recent studies argue that other physiological solutions are superior to normal saline, which is due to their physiological features, better outcomes in critical care, and lower risk of hyperchloremia and acidosis; nonetheless, it is still a mystery how normal saline has dominated the field of fluid therapy worldwide. Moreover, there is an ongoing debate on whether harm to human health may limit its spread in the future. Additionally, new evidence revealed some of the deleterious effects of normal saline, including coagulopathy, metabolic acidosis, acute kidney injury (AKI), and higher mortality in ICU. The predominant cause for these outcomes appears to be the excess chloride concentration of normal saline relative to plasma. Therefore, it appears relevant to suggest that a normal saline solution should be normalized to that of human serum to overcome these pitfalls. An ideal normal saline solution shall be similar to human serum in its pH, osmolarity, and content of sodium, chloride, and essential minerals.

Keywords

normal saline, acidic saline, balanced crystalloids, acidosis, hyperchloremia, diabetic acidosis, myalgia, hyperalgesia

Introduction

Normal saline, or physiological saline, as it is frequently called, is a 0.9% sodium chloride (NaCl) solution. It is mainly used to treat dehydration caused by various reasons and as a solvent for drugs in neurology and critical care clinics, where a large amount of experience has been gathered. Commercial normal saline contains 9 g of NaCl per liter, adjusted with hydrochloric acid (HCl) to a pH of around 5.5 [1]. Nonetheless, commercial normal saline is perhaps not normal in many ways [2], or simply, it is neither normal nor physiological [2–5]. Although of the acidic nature (pH 5.6) of normal commercial saline, it is hereafter referred to as normal saline. Normal saline is an unbuffered solution with a higher osmolarity of 308 milliosmoles per liter (mOsm/L) [6] than human serum of 285 (275 to 295) mOsm/L [7–9]. This

supraphysiologic chloride content may cause various adverse effects [9]. Figure 1 represents the formula structure of commercial saline (pH, osmolarity, and sodium and chloride concentration).

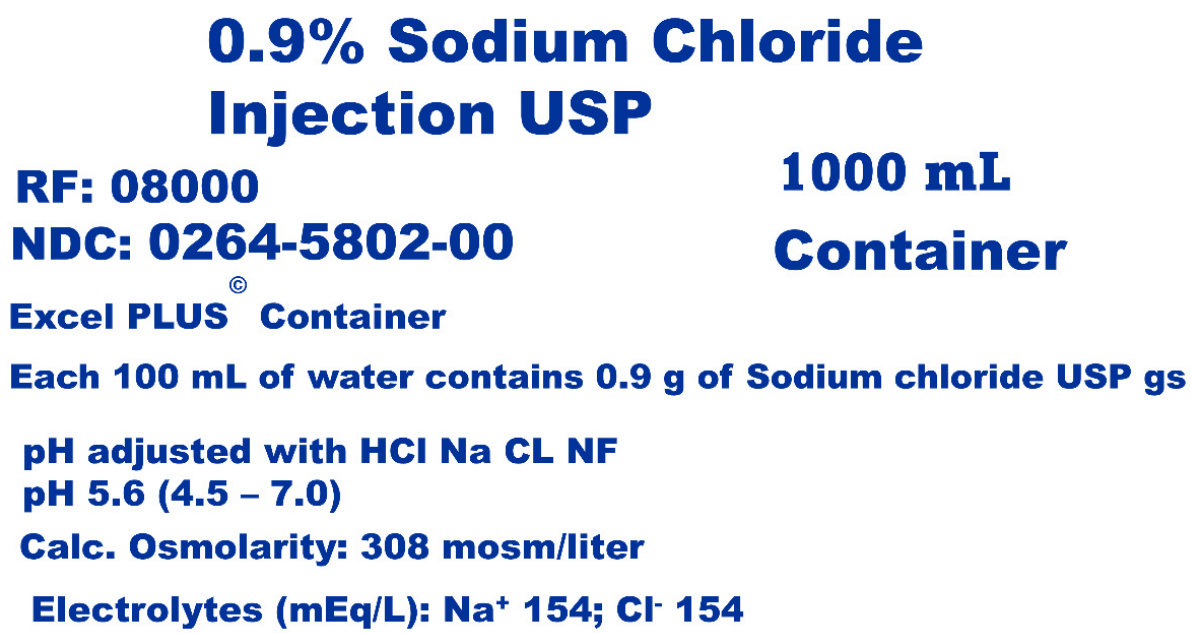

Figure 1. Normal saline formula structure. Osmolarity of 308 mOsm/L, pH 5.6 (4.5–7.0), and sodium and chloride concentrations of 154 mEq/L each. mEq/L: milliequivalents per liter; mOsm/L: milliosmoles per liter.

However, almost two centuries have elapsed since the controversial introduction of normal saline into clinical practice in 1831; it has come to dominate intravenous hydration and fluid resuscitation worldwide. Although a wide variety of side effects are associated with normal saline infusion, it is still a common practice in modern critical care medicine. While various physicians and scientists are aware of the harmful effects of acidic saline infusion on human health, the infiltration of this information to critical care physicians is still poor or lacking. Hence, the harmful effects of normal saline infusion on human health shall be emphasized during medical school education, so physicians may avoid this practice. Normal saline has a lower pH and higher osmolarity, sodium, and chloride concentration than human serum. Thus, it seems important to suggest that osmolarity, chloride and sodium concentration, and the pH of normal saline should be normalized to that of the human serum to avoid these pitfalls. Normal saline is mainly used to treat dehydration caused by various reasons and as a solvent for drugs in neurology and orthopedic surgery clinics (Figure 2). An ideal saline solution shall be similar to serum in its pH, osmolarity, and the content of sodium, chloride, and essential minerals. Once ideal saline solutions have been identified and their efficacy is tested, it is evident that normal saline will be replaced in favor of safer physiological solutions. Actually, balanced crystalloids, which are physiologically closer to plasma than normal saline, have been shown to reduce the composite outcome of death, initiation of renal-replacement therapy, or persistent renal dysfunction in critically ill adults. On the other hand, among critically ill patients requiring fluid challenges, the use of crystalloids compared with 0.9% saline solution did not significantly reduce 90-day mortality. This minireview highlights issues on the horizon of normal saline, enriches, and sparks the ongoing debate led by experts in the field of fluid therapy, like Santi and colleagues [10]. Furthermore, it underlines the various effects of normal saline on calcium homeostasis, induction of pain, and the physiology of blood, kidney, bone, muscle, heart, and brain.

Normal saline and calcium homeostasis

Calcium represents the fifth element in the human body, with about 1 kg in adults [11]. However, about 990 g of total body calcium is present in bone as a calcium phosphate complex (hydroxyapatite), the rest,

Figure 2. Normal saline applications in medical practice. Fluid resuscitation, including blood volume restoration (left side), or as a carrier fluid for administering medications and other intravenous therapies (right side).

~10 g, represents ionic calcium, ionic calcium complexes (calcium phosphate, calcium carbonate, and calcium oxalate), and protein-bound calcium (mainly albumin and globulin in serum), representing 40, 10, and 50% respectively [12]. Calcium plays an essential role in a wide range of biological functions, including bone extracellular matrix mineralization through either endochondral or intramembranous pathways. Calcium provides skeletal strength and serves as a reservoir for calcium release into serum through the parathyroid hormone (PTH) bone resorption pathway. Ionic (free) calcium (hereafter calcium) homeostasis is hormonally regulated by PTH, vitamin D3, and calcitonin [13].

Changes in pH have remarkable influences on calcium homeostasis [14]. Metabolic acidosis induces bone mineral resorption and inhibits osteoblast matrix mineralization in vitro [15, 16]. Hinkle and Cooperman [17] measured serum calcium concentration in a group of six patients after receiving citrated blood transfusions during general anesthesia. This study revealed an average decrease of 0.5 mg/100 mL or 0.6 mg/100 mL after 500 or 1,000 mL of citrated blood infusion, respectively. However, the calcium ion concentration increased by an average of 0.3 mg/100 mL (10 minutes after the transfusion of the citrated blood), indicating a rapid activation of the bone resorption pathway to release calcium into the bloodstream [18]. Therefore, it seems that there is no convincing rationale to use normal saline as the first choice for volume resuscitation of critically ill patients [2, 19]. Furthermore, a deficit of serum calcium due to poor dietary intake, or consumption of acidic drinks, such as soft drinks [20–25] is a detrimental factor to bone mineral density and teeth mineralization.

Normal saline induction of pain

Normal saline induction of pain in experimental animal models and humans [26–33], myalgia [34], and hyperalgesia [26, 35–39] are popular pain models in pain research. Animal models and clinical studies indicated that normal saline injections may cause metabolic acidosis, inflammation, chronic muscle and abdominal pain, and functional and structural organ damage [40–43], neuronal depolarization [44], vascular and renal function changes [2, 45], and fibromyalgia, which is often associated with various mental disorders including cognitive impairment, anxiety, and depression [46, 47]. In contrast, normal saline pH 7.4 [48], which is equal to serum pH, normal saline (pH 4.0) injection into mice gastrocnemius muscle induces chronic muscle hyperalgesia lasting over 2 weeks [35], which is mediated through acid sensing ion channel 3 [49]. While it is established that acidosis induces pain, acidosis signaling is linked to many elusive

chronic pain diseases [50]. Intravenous injection of vecuronium and normal saline (pH 4.08) mixture exacerbates pain in humans [51]. On the contrary, neutral fluid (pH 7.4) infusion into hand skin or interosseous muscle triggers no pain in complex regional pain syndrome patients or healthy controls [52].

Normal saline, blood, and organ physiology

Blood physiology

Blood roughly comprises 7% of body weight, and it contains plasma, red cells (erythrocytes), white cells (leukocytes), and platelets (thrombocytes). Healthy human blood pH is about 7.4, which is tightly regulated to remain within a minute range of 7.35 to 7.45 [2, 52–55]. Therefore, pH alterations beyond this range can be detrimental to cellular processes such as enzymatic functions that may lead to cellular death. Systemic blood acidity (acidemia) occurs when blood pH drops under 7.28 [56]. However, Khan and colleagues [57] reported that acidosis emerges when blood pH drops below 7.34. Normal saline absorption during transurethral and transcervical surgery leads to metabolic acidemia [58]. A major side effect of normal saline is hyperchloremic acidosis [59–62]. Low-grade metabolic acidosis reduces blood buffering capacity, leading to a greater reliance on muscle, bone, and connective tissue for the removal of residual acid [63]. Furthermore, Yang and colleagues [64] revealed that acidosis elicits tumorigenesis by activating the serine threonine kinase/nuclear factor-κB (Akt/NF-κB) signaling pathway. Lenert and colleagues [65] have proven that normal saline (pH 4.0) promotes T cell-mediated activation of B cells, enhances active plasma cells, increases memory B cells, and raises MHC class II-expressing B cells in peripheral blood, while reducing immunoglobulin G (IgG) levels in a model of chronic widespread pain in a female mouse model. However, therapy of blood acidosis using reduced osmolarity mixed-base solution having a 3:1 ratio of sodium carbonate: sodium bicarbonate or simply carb: bicarb (Na_2CO_3:$NaHCO_3$) has been achieved through raising plasma pH and serum bicarbonate concentration $[HCO_3]^-$ while reducing the partial pressure of CO_2; normally known as PCO_2 [66].

Kidney physiology

Kidneys are the main buffering system for removing acids and salts from the body. Acute metabolic acidosis decreases the functions of the kidneys as their ability to eliminate acids goes down with acid overload in the body, which impairs kidney function over long periods of time. In fact, chronic metabolic acidosis leads to nephron hypertrophy in animal models, which is due to ammonia's toxic effects on the kidneys. However, kidneys can remove a certain amount of acids daily before acid retention occurs due to acid overload [63]. Kidney acid overload leads to muscle and connective tissue breakdown to provide nitrogen for ammonia formation and calcium release from bone to avoid acid retention.

Authors have recently provided evidence of the deleterious effects of normal saline infusion in the emergency department, including increased mortality [67], acute kidney injury [10], metabolic acidosis, and coagulopathy, which is due to the higher chloride concentration of the normal saline [154 milliequivalents per liter (mEq/L)] relative to human serum of 96 to 106 mEq/L [68]. A multicenter retrospective study of heat stroke patients has revealed an association between the volume of normal saline infusion in the emergency departments and acute kidney injury [42, 43]. Moreover, sodium overload leads to an increase in blood pressure [69–72].

Bone physiology

Bone remodeling includes resorption and regeneration of new bone. An upsurge of serum calcium ions (Ca^{2+}) induces thyroid parafollicular cells (C cells) to release calcitonin, a 32-amino acid hormone. Calcitonin stimulates calcium deposition into bone and inhibits renal reabsorption of calcium, meanwhile restraining bone resorption.

Acidic serum stimulates parathyroid glands to produce PTH, which activates the bone resorption pathway and the release of calcium into the bloodstream. Calcium influx into bloodstreams restores serum pH to 7.4 and calcium concentration to a physiologic range of 88–104 mg/L [11]. Such fine-tuned calcium concentration is required for the body to maintain physiological functions [11, 73, 74]. PTH acts on the

kidneys to increase calcium reabsorption and induces bone resorption to release calcium into the bloodstream. Figure 3, left column, shows the effect of normal saline infusion on the bone resorption pathway through the activation of PTH. Consequently, PTH induces the receptor activator of NF-κB ligand (RANKL), RANK, and represses osteoprotegerin, the decoy factor of RANKL [73]. The kidney responds to PTH by increasing the release of vitamin D3, stimulating the intestines to absorb calcium, as seen in Figure 3, middle column. In fact, frequent consumption of soft drinks has similar bone catabolic effects in adolescents, including impaired bone mineral accrual and high bone fracture risk [20–25].

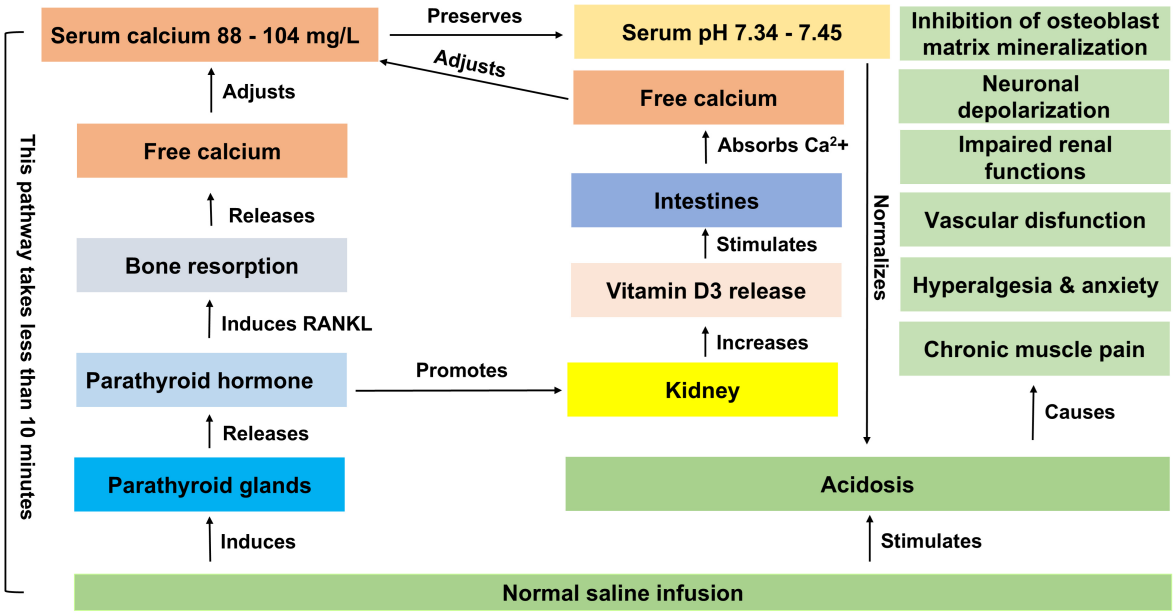

Figure 3. Normal saline effects on human health. Normal saline infusion induces acidosis and parathyroid glands to release parathyroid hormone. Parathyroid hormone induces RANKL to activate bone resorption and the release of free calcium into the bloodstream, which adjusts serum calcium concentration to a range of 88–104 mg/L. Such serum calcium concentration preserves serum pH to 7.34–7.45, leading to acidosis normalization. Parathyroid hormone promotes the kidneys to increase the release of vitamin D3, stimulating the intestine to absorb and infuse calcium into the serum. Acidosis causes chronic muscle pain, vascular dysfunction, impaired renal function, hyperalgesia/anxiety, neuronal depolarization, and inhibition of osteoblast matrix mineralization [86, 87].

Muscle physiology

Calcium plays an essential role in many events in the body, including cell growth, cell proliferation, programmed cell death (apoptosis), bone matrix mineralization, blood coagulation [10, 60], exocytosis, neuronal function, inflammation, nerve impulse transmission, and muscle contraction [11, 12, 75–80]. Normal saline (pH 4.0) intramuscular infusion induces hyperalgesia, chronic muscle pain, and muscle atrophy [39, 81, 82] as seen in Figure 3, right column. Intense hypocalcemia (less than 85 mg/L) may cause several medical indications, including congestive heart failure, muscle spasms and tetany, fatigue, depression, and seizures, among others [74].

In skeletal muscle, the effects of vitamin D are beyond calcium and phosphate homeostasis and bone health. Vitamin D deficiency is implicated in many neuromuscular diseases. Muscle weakness (myopathy), muscle pain (myalgia), bone pain (ostealgia), and hypotonia are commonly encountered among patients with vitamin D deficiency (e.g., rickets and osteomalacia). Muscle weakness noted in vitamin D deficiency is progressive and mostly appears in the proximal musculature [83, 84]. Metabolic acidosis affects muscle through several pathways, including inducing protein degradation while reducing protein synthesis, leading to muscle breakdown, preventing mitochondrial function, decreasing oxidative phosphorylation and energy production, and directly restricting muscle contraction [85].

Heart physiology

Using fluorescence multiphoton microscopy and biochemical techniques, Thatte and colleagues [86, 87] have found a direct correlation between low pH (< 7.0) and apoptosis in cardiac samples obtained from patients undergoing cardiac surgery. Acidosis leads to mechanical alterations in the ferret heart muscle [87]. Furthermore, acidosis of intracellular fluid reduces the contractility of the heart muscle due to its sensitivity to minor physiological decreases in extracellular pH [88]. A steady fall in the pH beyond 7.28 during normal saline infusion in animal models leads to declines in several measures of cardiac function, including global ejection fraction, the maximal rate of rise of left ventricular pressure (dPmax), stroke volume index, cardiac function index, cardiac power index, and cardiac index [56]. Preclinical studies in animal models have shown that systemic acidemia can impair cardiovascular function and weaken cardiac contractility [89], which may lead to heart failure [90–92]. Furthermore, intramuscular injection of normal saline (pH 4.0) triggers widespread pain and unbalanced cardiovascular dysfunctions [93].

Brain physiology

Acidosis is a normal aspect of the human brain during ischemic stroke and can cause neuronal injury, which is due to the activation of acid-sensing ion channels [94]. Severe acidosis (pH 6.2) potentiates neuronal apoptosis during cerebral ischemia, which may partially result from oxidative injury exacerbation [95, 96]. Moreover, neuronal loss is detected in the hippocampus of mice following prenatal injection of normal saline [97]. In reality, acidosis induces necrosis and apoptosis of cultured hippocampal neurons [98]. Also, it has been shown that lowering blood pH impairs the nervous system's excitability to electrical stimulation [99]. Additionally, acidosis may play an essential role in the development of vascular dementia (multi-infraction dementia) and Alzheimer disease [100]. Normal saline (pH 6.2) increases cytosolic calcium ions by stimulating calcium influx in the nucleus ambiguous neurons [44].

The blood-brain barrier (BBB) firmly controls the entry of molecules from plasma into the central nervous system (CNS) and plays a crucial role in appropriate CNS functions. BBB dysfunctions appear in several degenerative neurological disorders such as Alzheimer and Parkinson diseases, among others [101]. However, hyperosmolarity disrupts the BBB of male Wistar rat brains [102]. Furthermore, acidosis impairs brain functions through cortical gamma aminobutyric acid (GABA)ergic neurons deterioration [103, 104]. which is due to the dysfunction of cortical GABAergic neurons through astrocyte-intermediated excitotoxicity [105]. Additionally, acidosis causes neurological disorders via the overexcitation of cortical pyramidal neurons [106].

Guo and colleagues [107] have indicated that acidosis exercises its cytotoxic effects on HT22 neurons by promoting autophagic cell death through the acid-sensing ion channel 1 (ASIC1)-related Akt/mTOR signaling pathway [108]. Moreover, mouse colon sensory neurons sense extracellular acidosis through the transient receptor potential cation channel subfamily V member 1 (TRPV1) [108]. Pirchl and colleagues [100] have revealed that cholinergic neurons have a high capacity to recompense for pH perturbations. However, at a certain pH, cholinergic neurons show weakness, indicating that a low pH has deleterious effects on the brains of Alzheimer patients. Moreover, acidosis may exacerbate the deposition of β-amyloid peptide in the CNS and basal ganglia and contribute to Alzheimer and Parkinson disease pathogenesis [109, 110]. Furthermore, carbonated soft drinks increase oxidative stress and alter the expression of certain genes in the brain of Wistar rats (i.e., increase serum levels of malondialdehyde and dopamine D2 receptor, downregulate the expression of antioxidants glutathione reductase, catalase, glutathione peroxidase, monoamine oxidase A, and 5-hydroxytryptamine transporter, and acetylcholine esterase), which are related to brain activity [111].

Discussion

While normal saline is mainly used to treat dehydration caused by various reasons and as a solvent for drugs in neurology and orthopedic surgery clinics; nonetheless, some cautions on side effects have to be considered. The medical use of acidic saline in patient care for volume substitution and restoration, as well as hematology and transfusion medicine, began around 1831 [112, 113], which was initiated on the basis of

historic delusion and misconception [3]. However, it remains a historical mystery how it came to dominate intravenous infusion and fluid revitalization worldwide [114]. Furthermore, investigations of the composition of the fluids administered by pioneering physicians of that era, such as Thomas Aitchison Latta, reveal solutions without resemblance to normal saline, which indicate that normal saline may have very little scientific basis for its routine use in critical care medicine [3].

Normal saline has nearly 40% more chloride, 10% more sodium, and a lower pH (5.6 versus 7.4) than human serum [113]. Additionally, serum essential minerals are vital for innate and adaptive immune systems [115]. There are concerns about whether normal saline is the safest alternative for infusion therapy [2]. The effects of citrated blood transfusion on bone calcium depletion have been known for more than half a century [17]; nonetheless, normal saline transfusion is still a common practice in USA hospitals and around the world. Although infusion of normal saline can lead to metabolic acidemia, Reddi [1] has reported that the acidity of saline solution is unrelated to acidemia following normal saline infusion.

In animal models and clinical trials, normal saline infusion has been correlated with adverse events including microcirculation problems, acute kidney injury, adverse clinical outcomes, immunological disorders, endothelial activation, a greater inflammatory response, retinal degeneration, glaucoma [10, 15, 42, 116], and glycocalyx degradation among other side effects; all of which are caused by hyperchloremic acidosis [112, 117–118]. However, recent studies argue that other physiological solutions are superior to normal saline, which is due to their physiological characteristics, better outcomes in critical care, and lower risk of hyperchloremia and acidosis [9, 119, 120].

Shaw and colleagues [121] have reported major complications, mortality, and resource utilization after open abdominal surgery comparing 0.9% saline to Plasma-Lyte. Also, Waikar and Winkelmayer [122] believe that sparing intravenous chloride will save from kidney injury.

Furthermore, monoclonal antibodies (mAbs) that are dissolved in normal saline (pH ≤ 6.5) entirely form insoluble aggregates upon mixing with dextrose and serum. This aggregation was not feasible for the mAbs that are liquefied in neutral pH buffers (7.2–7.5) or in buffers containing NaCl with neutral pH [123], which has implications in selecting the right diluent for intravenous infusion of therapeutic mAbs.

Nonetheless, a Canadian crossover trial of hospital-wide lactated Ringer versus normal saline did not result in a meaningfully inferior incidence of death or readmission to the hospital within 90 days after the index admission [124–126]. Moreover, the same results were replicated in a multicenter, double-blind randomized clinical trial conducted in 75 ICUs in Brazil, including the randomization of approximately 11,000 patients to balanced crystalloids or saline groups [127].

Another randomized controlled trial comparing normal saline and lactated Ringer as intravenous fluid therapy in children with diabetic ketoacidosis (DKA) revealed that lactated Ringer can be carefully considered for the administration of pediatric DKA and may be ideal in patients that are at a risk of difficulties due to hyperchloremia [128], indicating that lactated Ringer may offer benefits over normal saline for the handling of patients with DKA [43].

Moreover, current evidence from clinical trials, observational research, and basic science research suggests that using balanced crystalloids such as lactated Ringer or plasma-lyte rather than normal saline may have valuable effects on patient outcomes, renal physiology, and acid-base balance [60, 129]. Nonetheless, the use of normal saline may be favored in certain clinical settings such as advanced liver disease, cerebral edema, and hyperkalemia with renal failure [130]. Also, lactated Ringer appears inappropriate for patients at risk for brain edema and for those with obvious or hidden chloride-deficiency [10]. In reality, Vanderbilt University Medical Center is encouraging physicians to stop using normal saline for intravenous fluid therapy for most patients, a change triggered by landmark clinical trials [131–136]. Yet, it seems that normal saline is a “problem”, not a “solution” [137]. Therefore, the fluid therapy debate shall continue until the characterization of ideal colloid and balanced crystalloids solutions has been fully attained [138–142].

Conclusions

While various adverse effects of normal saline have regularly been highlighted in scientific literature, its use remains common in clinical practice. The precision medicine strategy for fluid therapy should represent the ultimate principle for all patients, considering the best crystalloid therapy suitable for each patient. However, an ideal saline solution shall be like human serum in its pH, osmolarity, essential minerals (calcium, magnesium, potassium, iron, zinc, copper, and selenium), sodium, and chloride strengths. Therefore, until the formulation of this ideal saline solution, the great fluid debate shall continue. However, there is evidence that changing the pH of normal saline to 7.4 has a major effect in reducing the pain [52] and inhibits bone resorption.

Abbreviations

Akt: serine threonine kinase

BBB: blood-brain barrier

CNS: central nervous system

DKA: diabetic ketoacidosis

GABA: gamma aminobutyric acid

mAbs: monoclonal antibodies

mEq/L: milliequivalents per liter

mOsm/L: milliosmoles per liter

NaCl: sodium chloride

NF-κB: nuclear factor-κB

PTH: parathyroid hormone

RANKL: receptor activator of nuclear factor ligand

Declarations

Acknowledgments

Fawzy A. Saad is the founder of Galaxies Pharmaceuticals. The authors would like to thank Natalie B. Saad for reading the manuscript. The author asserts that the work presented within the manuscript is their own original creation and not under consideration for publication elsewhere.

Author contributions

JFS: Data curation, Formal analysis, Writing—review & editing. FAS: Conceptualization, Writing—original draft, Writing—review & editing, Supervision. Both authors read and approved the submitted version.

Conflicts of interest

The authors declare that there are no conflicts of interest.

Ethical approval

Not applicable.

Consent to participate

Not applicable.

Consent to publication

Not applicable.

Availability of data and materials

Not applicable.

Funding

There are no sources of financial assistance that were used to conduct the study or the analysis of the results described in the manuscript or used to assist with the preparation of the manuscript.

Publisher's note

Open Exploration maintains a neutral stance on jurisdictional claims in published institutional affiliations and maps. All opinions expressed in this article are the personal views of the author(s) and do not represent the stance of the editorial team or the publisher.

References

1. Reddi BA. Why is saline so acidic (and does it really matter?). Int J Med Sci. 2013;10:747–50. [DOI] [PubMed] [PMC]
2. Blumberg N, Cholette JM, Pietropaoli AP, Phipps R, Spinelli SL, Eaton MP, et al. 0.9% NaCl (Normal Saline) - Perhaps not so normal after all? Transfus Apher Sci. 2018;57:127–31. [DOI] [PubMed] [PMC]
3. Awad S, Allison SP, Lobo DN. The history of 0.9% saline. Clin Nutr. 2008;27:179–88. [DOI] [PubMed]
4. Li H, Sun SR, Yap JQ, Chen JH, Qian Q. 0.9% saline is neither normal nor physiological. J Zhejiang Univ Sci B. 2016;17:181–7. [DOI] [PubMed] [PMC]
5. Rasouli M. Why 0.9% saline is not normal. Pediatr Nephrol. 2019;34:1301–2. [DOI] [PubMed]
6. Rasouli M. Basic concepts and practical equations on osmolality: Biochemical approach. Clin Biochem. 2016;49:936–41. [DOI] [PubMed]
7. Weinberg L, Collins N, Van Mourik K, Tan C, Bellomo R. Plasma-Lyte 148: A clinical review. World J Crit Care Med. 2016;5:235–50. [DOI] [PubMed] [PMC]
8. Han K, Lee JY, Shin JE, Kim CH. Positional alcohol nystagmus and serum osmolality: New insights into dizziness associated with acute alcohol intoxication. Med Hypotheses. 2020;138:109606. [DOI] [PubMed]
9. Juncos LA, Connor MJ. Physiologic Solutions are Superior to Normal Saline in Critically Ill Patients: PRO. Kidney360. 2025;6:1270–2. [DOI] [PubMed] [PMC]
10. Santi M, Lava SA, Camozzi P, Giannini O, Milani GP, Simonetti GD, et al. The great fluid debate: saline or so-called "balanced" salt solutions? Ital J Pediatr. 2015;41:47. [DOI] [PubMed] [PMC]
11. Peacock M. Calcium metabolism in health and disease. Clin J Am Soc Nephrol. 2010;5 Suppl 1: S23–30. [DOI] [PubMed]
12. Hamroun A, Pekar JD, Lionet A, Ghulam A, Maboudou P, Mercier A, et al. Ionized calcium: analytical challenges and clinical relevance. J Lab Precis Med. 2020;5:22. [DOI]
13. Höffken B, Parkinson DK, Storms P, Radde IC. Effects of alterations of blood pH on calcium ion activity in rat plasma. Clin Orthop Relat Res. 1971;78:30–9. [DOI] [PubMed]
14. Gaiter AM, Bonfant G, Manes M, Belfanti P, Alloatti S. Relation between blood pH and ionized calcium during acute metabolic alteration of the acid-base balance in vivo. Scand J Clin Lab Invest. 1997;57: 317–23. [DOI] [PubMed]
15. Sprague SM, Krieger NS, Bushinsky DA. Greater inhibition of in vitro bone mineralization with metabolic than respiratory acidosis. Kidney Int. 1994;46:1199–206. [DOI] [PubMed]
16. Ori Y, Lee SG, Krieger NS, Bushinsky DA. Osteoblastic intracellular pH and calcium in metabolic and respiratory acidosis. Kidney Int. 1995;47:1790–6. [DOI] [PubMed]

17. Hinkle JE, Cooperman LH. Serum ionized calcium changes following citrated blood transfusion in anaesthetized man. Br J Anaesth. 1971;43:1108–12. [DOI] [PubMed]
18. Bunker JP. Metabolic effects of blood transfusion. Anesthesiology. 1966;27:446–55. [DOI] [PubMed]
19. Semler MW, Rice TW. Saline Is Not the First Choice for Crystalloid Resuscitation Fluids. Crit Care Med. 2016;44:1541–4. [DOI] [PubMed] [PMC]
20. McGartland C, Robson PJ, Murray L, Cran G, Savage MJ, Watkins D, et al. Carbonated soft drink consumption and bone mineral density in adolescence: the Northern Ireland Young Hearts project. J Bone Miner Res. 2003;18:1563–9. [DOI] [PubMed]
21. Ma D, Jones G. Soft drink and milk consumption, physical activity, bone mass, and upper limb fractures in children: a population-based case-control study. Calcif Tissue Int. 2004;75:286–91. [DOI] [PubMed]
22. Libuda L, Alexy U, Remer T, Stehle P, Schoenau E, Kersting M. Association between long-term consumption of soft drinks and variables of bone modeling and remodeling in a sample of healthy German children and adolescents. Am J Clin Nutr. 2008;88:1670–7. [DOI] [PubMed]
23. Høstmark AT, Søgaard AJ, Alvær K, Meyer HE. The oslo health study: a dietary index estimating frequent intake of soft drinks and rare intake of fruit and vegetables is negatively associated with bone mineral density. J Osteoporos. 2011;2011:102686. [DOI] [PubMed] [PMC]
24. Nikolić R, Kaličanin B, Krstić N. The release of zinc, copper, lead, and cadmium from the mineral tissue of teeth under the influence of soft drinks and sour-tasting food. Connect Tissue Res. 2012;53:229–35. [DOI] [PubMed]
25. Chen L, Liu R, Zhao Y, Shi Z. High Consumption of Soft Drinks Is Associated with an Increased Risk of Fracture: A 7-Year Follow-Up Study. Nutrients. 2020;12:530. [DOI] [PubMed] [PMC]
26. Sluka KA, Kalra A, Moore SA. Unilateral intramuscular injections of acidic saline produce a bilateral, long-lasting hyperalgesia. Muscle Nerve. 2001;24:37–46. [DOI] [PubMed]
27. Skyba DA, King EW, Sluka KA. Effects of NMDA and non-NMDA ionotropic glutamate receptor antagonists on the development and maintenance of hyperalgesia induced by repeated intramuscular injection of acidic saline. Pain. 2002;98:69–78. [DOI] [PubMed]
28. Radhakrishnan R, Bement MK, Skyba D, Sluka KA, Kehl LJ. Models of muscle pain: carrageenan model and acidic saline model. Curr Protoc Pharmacol. 2004;Chapter 5:Unit 5.35. [DOI] [PubMed]
29. Da Silva LF, Desantana JM, Sluka KA. Activation of NMDA receptors in the brainstem, rostral ventromedial medulla, and nucleus reticularis gigantocellularis mediates mechanical hyperalgesia produced by repeated intramuscular injections of acidic saline in rats. J Pain. 2010;11:378–87. [DOI] [PMC]
30. Sluka KA, O'Donnell JM, Danielson J, Rasmussen LA. Regular physical activity prevents development of chronic pain and activation of central neurons. J Appl Physiol (1985). 2013;114:725–33. [DOI] [PubMed] [PMC]
31. Louca S, Ernberg M, Christidis N. Influence of intramuscular granisetron on experimentally induced muscle pain by acidic saline. J Oral Rehabil. 2013;40:403–12. [DOI] [PubMed]
32. Sugimura N, Ikeuchi M, Izumi M, Kawano T, Aso K, Kato T, et al. Repeated intra-articular injections of acidic saline produce long-lasting joint pain and widespread hyperalgesia. Eur J Pain. 2015;19:629–38. [DOI] [PubMed]
33. Louca Jounger S, Eriksson N, Lindskog H, Oscarsson A, Simonsson V, Ernberg M, et al. Repeated buffered acidic saline infusion in the human masseter muscle as a putative experimental pain model. Sci Rep. 2019;9:15474. [DOI] [PubMed] [PMC]
34. Castrillon EE, Cairns B, List T, Svensson P, Ernberg M. Acidic saline-induced pain as a model for experimental masseter myalgia in healthy subjects. Eur J Pain. 2013;17:1438–46. [DOI] [PubMed]
35. Sharma NK, Ryals JM, Liu H, Liu W, Wright DE. Acidic saline-induced primary and secondary mechanical hyperalgesia in mice. J Pain. 2009;10:1231–41. [DOI] [PubMed] [PMC]

36. Jasper LL, MacNeil BJ. Diverse sensory inputs permit priming in the acidic saline model of hyperalgesia. Eur J Pain. 2012;16:966–73. [DOI] [PubMed] [PMC]
37. Wang K, Luo Y, Asaki T, Graven-Nielsen T, Cairns BE, Arendt-Nielsen T, et al. Acid-induced experimental muscle pain and hyperalgesia with single and repeated infusion in human forearm. Scand J Pain. 2017;17:260–6. [DOI] [PubMed]
38. Asaki T, Wang K, Luo Y, Arendt-Nielsen T, Graven-Nielsen T, Arendt-Nielsen L. Acid-induced experimental knee pain and hyperalgesia in healthy humans. Exp Brain Res. 2018;236:587–98. [DOI] [PubMed]
39. Choi GJ, Kang H, Lee OH, Ahn EJ, White FA, Cho YJ, et al. Effectiveness of maturity of Rubus occidentalis on hyperalgesia induced by acidic saline injection in rats. BMC Complement Med Ther. 2022;22:12. [DOI] [PubMed] [PMC]
40. Chen L, Liu C, Zhang Z, Zhang Y, Feng X. Effects of normal saline versus lactated Ringer's solution on organ function and inflammatory responses to heatstroke in rats. J Intensive Care. 2024;12:39. [DOI] [PubMed] [PMC]
41. Stellwagen E, Babul J. Stabilization of the globular structure of ferricytochrome c by chloride in acidic solvents. Biochemistry. 1975;14:5135–40. [DOI] [PubMed]
42. Tsuang FY, Wu YL, Chan KC, Lee CT, Wu CY. An Exploratory Randomized Controlled Trial of 0.9% Saline Versus Lactated Ringer's Solution on Intraoperative Metabolism Among Patients Undergoing Lumbar Spinal Surgery. Int J Med Sci. 2026;23:1002–14. [DOI] [PubMed] [PMC]
43. Jamison A, Mohamed A, Chedester C, Klindworth K, Hamarshi M, Sembroski E. Lactated Ringer's versus normal saline in the management of acute diabetic ketoacidosis (RINSE-DKA). Pharmacotherapy. 2024;44:623–30. [DOI] [PubMed]
44. Brailoiu GC, Deliu E, Altmann JB, Chitravanshi V, Brailoiu E. Evidence for role of acid-sensing ion channels in nucleus ambiguus neurons: essential differences in anesthetized versus awake rats. J Comp Physiol B. 2014;184:753–61. [DOI] [PubMed] [PMC]
45. Shaw AD, Bagshaw SM, Goldstein SL, Scherer LA, Duan M, Schermer CR, Kellum JA. Major complications, mortality, and resource utilization after open abdominal surgery: 0.9% saline compared to Plasma-Lyte. Ann Surg. 2012;255:821–9. [DOI] [PubMed]
46. Murasawa H, Kobayashi H, Yasuda SI, Saeki K, Domon Y, Arakawa N, et al. Anxiolytic-like effects of mirogabalin, a novel ligand for $\alpha_2\delta$ ligand of voltage-gated calcium channels, in rats repeatedly injected with acidic saline intramuscularly, as an experimental model of fibromyalgia. Pharmacol Rep. 2020;72:571–9. [DOI] [PubMed]
47. Murasawa H, Pawlak A, Kobayashi H, Saeki K, Yasuda SI, Kitano Y. Mirogabalin, a novel ligand for $\alpha_2\delta$ subunit of voltage-gated calcium channels, improves cognitive impairments in repeated intramuscular acidic saline injection model rats, an experimental model of fibromyalgia. Biomed Pharmacother. 2021;139:111647. [DOI] [PubMed]
48. Newman MR, Benoit DSW. In Vivo Translation of Peptide-Targeted Drug Delivery Systems Discovered by Phage Display. Bioconjug Chem. 2018;29:2161–9. [DOI] [PubMed] [PMC]
49. Sluka KA, Price MP, Breese NM, Stucky CL, Wemmie JA, Welsh MJ. Chronic hyperalgesia induced by repeated acid injections in muscle is abolished by the loss of ASIC3, but not ASIC1. Pain. 2003;106: 229–39. [DOI] [PubMed]
50. Hung C, Chin Y, Fong Y, Lee C, Han D, Lin J, et al. Acidosis-related pain and its receptors as targets for chronic pain. Pharmacol Ther. 2023;247:108444. [DOI] [PubMed]
51. Chow LH, Ho CM, Yang YC, Lee TY, Lui PW. Vecuronium dissolved in normal saline exaggerates pain on intravenous injection. Zhonghua Yi Xue Za Zhi (Taipei). 1995;55:315–8. [PubMed]
52. Birklein F, Weber M, Ernst M, Riedl B, Neundörfer B, Handwerker HO. Experimental tissue acidosis leads to increased pain in complex regional pain syndrome (CRPS). Pain. 2000;87:227–34. [DOI] [PubMed]

53. Janjua NK, Siddiqa A, Yaqub A, Sabahat S, Qureshi R, ul Haque S. Spectrophotometric analysis of flavonoid-DNA binding interactions at physiological conditions. Spectrochim Acta A Mol Biomol Spectrosc. 2009;74:1135–7. [DOI] [PubMed]
54. Temerk Y, Ibrahim M, Ibrahim H, Kotb M. Interactions of an anticancer drug Formestane with single and double stranded DNA at physiological conditions. J Photochem Photobiol B. 2015;149:27–36. [DOI] [PubMed]
55. Hopkins E, Sanvictores T, Sharma S. Physiology, Acid Base Balance. Treasure Island (FL): StatPearls Publishing; 2022. [PubMed]
56. Rodríguez-Villar S, Kraut JA, Arévalo-Serrano J, Sakka SG, Harris C, Awad I, et al.; Acid-Base Working Group. Systemic acidemia impairs cardiac function in critically Ill patients. EClinicalMedicine. 2021; 37:100956. [DOI] [PubMed] [PMC]
57. Reusch HP, Reusch R, Rosskopf D, Siffert W, Mann JF, Luft FC. Na+/H+ exchange in human lymphocytes and platelets in chronic and subacute metabolic acidosis. J Clin Invest. 1993;92:858–65. [DOI] [PubMed] [PMC]
58. Nakamura M, Ikeda K, Uezono S. Metabolic acidemia due to saline absorption during transurethral and transcervical surgery: a report of 2 cases. BMC Anesthesiol. 2024;24:62. [DOI] [PubMed] [PMC]
59. Barker ME. 0.9% saline induced hyperchloremic acidosis. J Trauma Nurs. 2015;22:111–6. [DOI] [PubMed]
60. Hoorn EJ. Intravenous fluids: balancing solutions. J Nephrol. 2017;30:485–92. [DOI] [PubMed] [PMC]
61. Semler MW, Kellum JA. Balanced Crystalloid Solutions. Am J Respir Crit Care Med. 2019;199:952–60. [DOI] [PubMed] [PMC]
62. Messina N, Anderson Z, Saravis L, Jimenez G, Plowman K, Harrington D. Revisiting Diabetic Ketoacidosis (DKA) Fluid Management: Should Normal Saline Be Used? Cureus. 2025;17:e77739. [DOI] [PubMed] [PMC]
63. DiNicolantonio JJ, O'Keefe J. Low-grade metabolic acidosis as a driver of chronic disease: a 21st century public health crisis. Open Heart. 2021;8:e001730. [DOI] [PubMed] [PMC]
64. Yang L, Hu X, Mo Y. Acidosis promotes tumorigenesis by activating AKT/NF-κB signaling. Cancer Metastasis Rev. 2019;38:179–88. [DOI] [PubMed]
65. Lenert ME, Green AR, Merriwether EN, Burton MD. B-cell and plasma cell activation in a mouse model of chronic muscle pain. Neurobiol Pain. 2024;16:100169. [DOI] [PubMed] [PMC]
66. Mason TG, Kraut JA. Treatment of Acidified Blood Using Reduced Osmolarity Mixed-Base Solutions. Front Physiol. 2016;7:625. [DOI] [PubMed] [PMC]
67. Hammond NE, Zampieri FG, Di Tanna GL, Garside T, Adigbli D, Cavalcanti AB, et al. Balanced Crystalloids versus Saline in Critically Ill Adults - A Systematic Review with Meta-Analysis. NEJM Evid. 2022;1:EVIDoa2100010. [DOI] [PubMed]
68. Hayes W. Ab-normal saline in abnormal kidney function: risks and alternatives. Pediatr Nephrol. 2019;34:1191–9. [DOI] [PubMed] [PMC]
69. Feuerstein G, Boonyaviroj P, Gutman Y. The effect of saline loading on blood pressure and catecholamine secretion in the rat and the cat. Eur J Pharmacol. 1979;54:373–82. [DOI] [PubMed]
70. Luft FC, Rankin LI, Bloch R, Willis LR, Fineberg NS, Weinberger MH. The effects of rapid saline infusion on sodium excretion, renal function, and blood pressure at different sodium intakes in man. Am J Kidney Dis. 1983;2:464–70. [DOI] [PubMed]
71. Wu J, Nie J, Wang Y, Zhang Y, Wu D. Relationship between saline infusion and blood pressure variability in non-critically patients with hypertension: A retrospective study. Medicine (Baltimore). 2020;99:e21468. [DOI] [PubMed] [PMC]
72. Kim GH. Primary Role of the Kidney in Pathogenesis of Hypertension. Life (Basel). 2024;14:119. [DOI] [PubMed] [PMC]

73. Saad FA. Novel insights into the complex architecture of osteoporosis molecular genetics. Ann N Y Acad Sci. 2020;1462:37–52. [DOI] [PubMed]
74. Yu E, Sharma S. Physiology, Calcium. Treasure Island (FL): StatPearls Publishing; 2023.
75. Dekker SE, Sillesen M, Bambakidis T, Jin G, Liu B, Boer C, et al. Normal saline influences coagulation and endothelial function after traumatic brain injury and hemorrhagic shock in pigs. Surgery. 2014; 156:556–63. [DOI] [PubMed]
76. Cheng H, Wei S, Wei L, Verkhratsky A. Calcium signaling in physiology and pathophysiology. Acta Pharmacol Sin. 2006;27:767–72. [DOI] [PubMed]
77. Allgrove J. Physiology of Calcium, Phosphate, Magnesium and Vitamin D. Endocr Dev. 2015;28:7–32. [DOI] [PubMed]
78. Pinto MC, Kihara AH, Goulart VA, Tonelli FM, Gomes KN, Ulrich H, et al. Calcium signaling and cell proliferation. Cell Signal. 2015;27:2139–49. [DOI] [PubMed]
79. Klein GL. The Role of Calcium in Inflammation-Associated Bone Resorption. Biomolecules. 2018;8: 69. [DOI] [PubMed] [PMC]
80. Talotta R, Rucci F, Scaglione F. Calcium physiology, metabolism and supplementation: a glance at patients with ankylosing spondylitis. Reumatologia. 2020;58:297–311. [DOI] [PubMed] [PMC]
81. Choi GJ, Kang H, Kim WJ, Baek CW, Jung YH, Woo YC, et al. Rubus occidentalis alleviates hyperalgesia induced by repeated intramuscular injection of acidic saline in rats. BMC Complement Altern Med. 2016;16:202. [DOI] [PubMed] [PMC]
82. Costa DM, da Silva RP, da Cruz-Filho J, de Oliveira Santos T, Dos Anjos-Santos HC, de Lucca W Jr, et al. Adrenalectomy attenuates hyperalgesia but does not regulate muscle wasting in a female rat model of fibromyalgia. Clin Exp Pharmacol Physiol. 2024;51:e13837. [DOI] [PubMed]
83. Schott GD, Wills MR. Muscle weakness in osteomalacia. Lancet. 1976;1:626–9. [DOI] [PubMed]
84. Russell JA. Osteomalacic myopathy. Muscle Nerve. 1994;17:578–80. [DOI] [PubMed]
85. Ho JQ, Abramowitz MK. Clinical Consequences of Metabolic Acidosis-Muscle. Adv Chronic Kidney Dis. 2022;29:395–405. [DOI] [PubMed]
86. Thatte HS, Rhee J, Zagarins SE, Treanor PR, Birjiniuk V, Crittenden MD, et al. Acidosis-induced apoptosis in human and porcine heart. Ann Thorac Surg. 2004;77:1376–83. [DOI] [PubMed]
87. Orchard CH, McCall E, Kirby MS, Boyett MR. Mechanical alternans during acidosis in ferret heart muscle. Circ Res. 1991;68:69–76. [DOI] [PubMed]
88. Poole-Wilson PA. Acidosis and contractility of heart muscle. Ciba Found Symp. 1982;87:58–76. [DOI] [PubMed]
89. Frasch MG, Giussani DA. Heart during acidosis: Etiology and early detection of cardiac dysfunction. EClinicalMedicine. 2021;37:100994. [DOI] [PubMed] [PMC]
90. Ozawa H, Homma Y, Arisawa H, Fukuuchi F, Handa S. Severe metabolic acidosis and heart failure due to thiamine deficiency. Nutrition. 2001;17:351–2. [DOI] [PubMed]
91. Blanc P, Henriette K, Boussuges A. Severe metabolic acidosis and heart failure due to thiamine deficiency. Nutrition. 2002;18:118. [DOI] [PubMed]
92. Miller JD, Hemauer SJ, Smith CA, Stickland MK, Dempsey JA. Expiratory threshold loading impairs cardiovascular function in health and chronic heart failure during submaximal exercise. J Appl Physiol (1985). 2006;101:213–27. [DOI] [PubMed]
93. Oliveira LR, de Melo VU, Macedo FN, Barreto AS, Badaue-Passos D Jr, Viana dos Santos MR, et al. Induction of chronic non-inflammatory widespread pain increases cardiac sympathetic modulation in rats. Auton Neurosci. 2012;167:45–9. [DOI] [PubMed] [PMC]
94. Li M, Inoue K, Branigan D, Kratzer E, Hansen JC, Chen JW, et al. Acid-sensing ion channels in acidosis-induced injury of human brain neurons. J Cereb Blood Flow Metab. 2010;30:1247–60. [DOI] [PubMed] [PMC]

95. Goldman SA, Pulsinelli WA, Clarke WY, Kraig RP, Plum F. The effects of extracellular acidosis on neurons and glia in vitro. J Cereb Blood Flow Metab. 1989;9:471–7. [DOI] [PubMed] [PMC]
96. Ying W, Han SK, Miller JW, Swanson RA. Acidosis potentiates oxidative neuronal death by multiple mechanisms. J Neurochem. 1999;73:1549–56. [DOI] [PubMed]
97. Schmitz C, Bültmann E, Gube M, Korr H. Neuron loss in the mouse hippocampus following prenatal injection of tritiated thymidine or saline. Int J Dev Neurosci. 1999;17:185–90. [DOI] [PubMed]
98. Ding D, Moskowitz SI, Li R, Lee SB, Esteban M, Tomaselli K, et al. Acidosis induces necrosis and apoptosis of cultured hippocampal neurons. Exp Neurol. 2000;162:1–12. [DOI] [PubMed]
99. WINDLE WF, KOENIG H, JENSEN AV. Histologic study of the brain in experimentally induced acidosis. Arch Neurol Psychiatry. 1946;56:428–33. [DOI] [PubMed]
100. Pirchl M, Marksteiner J, Humpel C. Effects of acidosis on brain capillary endothelial cells and cholinergic neurons: relevance to vascular dementia and Alzheimer's disease. Neurol Res. 2006;28:657–64. [DOI] [PubMed]
101. Zhao Z, Nelson AR, Betsholtz C, Zlokovic BV. Establishment and Dysfunction of the Blood-Brain Barrier. Cell. 2015;163:1064–78. [DOI] [PubMed] [PMC]
102. Chi OZ, Hunter C, Liu X, Tan T, Weiss HR. Effects of VEGF on the blood-brain barrier disruption caused by hyperosmolarity. Pharmacology. 2008;82:187–92. [DOI] [PubMed]
103. Li F, Liu X, Su Z, Sun R. Acidosis leads to brain dysfunctions through impairing cortical GABAergic neurons. Biochem Biophys Res Commun. 2011;410:775–9. [DOI] [PubMed]
104. Song R, Zhang L, Yang Z, Tian X. Acidosis and alkalosis impair brain functions through weakening spike encoding at cortical GABAergic neurons. J Neurol Sci. 2011;304:122–6. [DOI] [PubMed]
105. Huang L, Zhao S, Lu W, Guan S, Zhu Y, Wang J. Acidosis-Induced Dysfunction of Cortical GABAergic Neurons through Astrocyte-Related Excitotoxicity. PLoS One. 2015;10:e0140324. [DOI] [PubMed] [PMC]
106. Zhao H, Cai Y, Yang Z, He D, Shen B. Acidosis leads to neurological disorders through overexciting cortical pyramidal neurons. Biochem Biophys Res Commun. 2011;415:224–8. [DOI] [PubMed]
107. Guo M, Qiu M, Zeng L, Nie Y, Tang Y, Luo Y, et al. Acidosis induces autophagic cell death through ASIC1-mediated Akt/mTOR signaling in HT22 neurons. Toxicology. 2025;511:154045. [DOI] [PubMed]
108. Sugiura T, Bielefeldt K, Gebhart GF. Mouse colon sensory neurons detect extracellular acidosis via TRPV1. Am J Physiol Cell Physiol. 2007;292:C1768–74. [DOI] [PubMed]
109. Pluta R, Kida E, Lossinsky AS, Golabek AA, Mossakowski MJ, Wisniewski HM. Complete cerebral ischemia with short-term survival in rats induced by cardiac arrest. I. Extracellular accumulation of Alzheimer's beta-amyloid protein precursor in the brain. Brain Res. 1994;649:323–8. [DOI] [PubMed]
110. Brewer GJ. Effects of acidosis on the distribution of processing of the beta-amyloid precursor protein in cultured hippocampal neurons. Mol Chem Neuropathol. 1997;31:171–86. [DOI] [PubMed]
111. El-Terras A, Soliman MM, Alkhedaide A, Attia HF, Alharthy A, Banaja AE. Carbonated soft drinks induce oxidative stress and alter the expression of certain genes in the brains of Wistar rats. Mol Med Rep. 2016;13:3147–54. [DOI] [PubMed]
112. Latta T. Letter from Dr. Latta to the Secretary of the Central Board of Health, London, affording a view of the rationale and results of his practice in the treatment of cholera by aqueous and saline injections. 1832. Int J Epidemiol. 2013;42:387–90. [DOI] [PubMed]
113. Fernández-Sarmiento J, Casas-Certain C, Ferro-Jackaman S, Solano-Vargas FH, Domínguez-Rojas JÁ, Pilar-Orive FJ. A brief history of crystalloids: the origin of the controversy. Front Pediatr. 2023;11:1202805. [DOI] [PubMed] [PMC]
114. Liu X, Lu M. Normal saline: Past, present, and future. Sci Prog. 2023;106:368504231168821. [DOI] [PubMed] [PMC]

115. Stefanache A, Lungu I, Butnariu I, Calin G, Gutu C, Marcu C, et al. Understanding How Minerals Contribute to Optimal Immune Function. J Immunol Res. 2023;2023:3355733. [DOI] [PubMed] [PMC]
116. Hombrebueno JR, Luo C, Guo L, Chen M, Xu H. Intravitreal Injection of Normal Saline Induces Retinal Degeneration in the C57BL/6J Mouse. Transl Vis Sci Technol. 2014;3:3. [DOI] [PubMed] [PMC]
117. Rhee P, Wang D, Ruff P, Austin B, DeBraux S, Wolcott K, et al. Human neutrophil activation and increased adhesion by various resuscitation fluids. Crit Care Med. 2000;28:74–8. [DOI] [PubMed]
118. Williams RN, Hj Ibrahim N, Nunes Q M, Allison SP, Rowlands BJ, Adrian Robins R, et al. Effect of intravenous infusion of 0.9% saline on neutrophil activation in healthy volunteers. J Organ Dysfunction. 2006;2:166e72. [DOI]
119. Fenves AZ, Allegretti AS. Physiologic Solutions are Superior to Normal Saline in Critically Ill Patients: CON. Kidney360. 2025;6:1273–5. [DOI] [PubMed] [PMC]
120. Sanghavi SF. Physiologic Solutions are Superior to Normal Saline in Critically Ill Patients: Commentary. Kidney360. 2025;6:1276–7. [DOI] [PubMed] [PMC]
121. Diz JC, Luna-Rojas P, Díaz-Vidal P, Fernández-Vázquez U, Gil-Casado C, Diz-Ferreira E. Effect of Treatment With Balanced Crystalloids Versus Normal Saline on the Mortality of Critically Ill Patients With and Without Traumatic Brain Injury: A Systematic Review and Meta-Analysis. Anesth Analg. 2025;141:152–61. [DOI] [PubMed]
122. Waikar SS, Winkelmayer WC. Saving the kidneys by sparing intravenous chloride? JAMA. 2012;308:1583–5. [DOI] [PubMed]
123. Luo S, McSweeney KM, Wang T, Bacot SM, Feldman GM, Zhang B. Defining the right diluent for intravenous infusion of therapeutic antibodies. MAbs. 2020;12:1685814. [DOI] [PubMed] [PMC]
124. Ince C, Groeneveld AB. The case for 0.9% NaCl: is the undefendable, defensible? Kidney Int. 2014;86:1087–95. [DOI] [PubMed]
125. Mayerhöfer T, Shaw AD, Wiedermann CJ, Joannidis M. Fluids in the ICU: which is the right one? Nephrol Dial Transplant. 2023;38:1603–12. [DOI] [PubMed] [PMC]
126. McIntyre L, Fergusson D, McArdle T, English S, Cook DJ, Fox-Robichaud AE, et al.; Canadian Critical Care Trials Group. A Crossover Trial of Hospital-Wide Lactated Ringer's Solution versus Normal Saline. N Engl J Med. 2025;393:660–70. [DOI] [PubMed]
127. Zampieri FG, Machado FR, Biondi RS, Freitas FGR, Veiga VC, Figueiredo RC, et al.; BaSICS investigators and the BRICNet members. Effect of Intravenous Fluid Treatment With a Balanced Solution vs 0.9% Saline Solution on Mortality in Critically Ill Patients: The BaSICS Randomized Clinical Trial. JAMA. 2021;326:1–12. [DOI] [PubMed] [PMC]
128. Singhal D, Gupta S, Kumar V. Normal Saline Versus Ringer's Lactate for Intravenous Fluid Therapy in Children with Diabetic Ketoacidosis: A Randomized Controlled Trial. Indian J Pediatr. 2025;92:1181–7. [DOI] [PubMed]
129. Salinero A, Mitzova-Vladinov G. Battle of the Crystalloids in the Operating Room: A Literature Review. J Perianesth Nurs. 2021;36:629–37. [DOI] [PubMed]
130. Mikhael B, Steele DJR, Fenves AZ. In Defense of Normal Saline: Our Perspective. Clin J Am Soc Nephrol. 2022;17:588–90. [DOI] [PubMed] [PMC]
131. Self WH, Semler MW, Wanderer JP, Ehrenfeld JM, Byrne DW, Wang L, et al. Saline versus balanced crystalloids for intravenous fluid therapy in the emergency department: study protocol for a cluster-randomized, multiple-crossover trial. Trials. 2017;18:178. [DOI] [PubMed] [PMC]
132. Semler MW, Wanderer JP, Ehrenfeld JM, Stollings JL, Self WH, Siew ED, et al.; SALT Investigators* and the Pragmatic Critical Care Research Group; SALT Investigators. Balanced Crystalloids versus Saline in the Intensive Care Unit. The SALT Randomized Trial. Am J Respir Crit Care Med. 2017;195:1362–72. [DOI] [PubMed] [PMC]

133. Semler MW, Self WH, Wang L, Byrne DW, Wanderer JP, Ehrenfeld JM, et al.; Isotonic Solutions and Major Adverse Renal Events Trial (SMART) Investigators; Pragmatic Critical Care Research Group. Balanced crystalloids versus saline in the intensive care unit: study protocol for a cluster-randomized, multiple-crossover trial. Trials. 2017;18:129. [DOI] [PubMed] [PMC]
134. Semler MW, Self WH, Wanderer JP, Ehrenfeld JM, Wang L, Byrne DW, et al.; SMART Investigators and the Pragmatic Critical Care Research Group. Balanced Crystalloids versus Saline in Critically Ill Adults. N Engl J Med. 2018;378:829–39. [DOI] [PubMed] [PMC]
135. Self WH, Semler MW, Wanderer JP, Wang L, Byrne DW, Collins SP, et al.; SALT-ED Investigators. Balanced Crystalloids versus Saline in Noncritically Ill Adults. N Engl J Med. 2018;378:819–28. [DOI] [PubMed] [PMC]
136. Brown RM, Wang L, Coston TD, Krishnan NI, Casey JD, Wanderer JP, et al. Balanced Crystalloids versus Saline in Sepsis. A Secondary Analysis of the SMART Clinical Trial. Am J Respir Crit Care Med. 2019;200:1487–95. [DOI] [PubMed] [PMC]
137. Lobo DN. Intravenous 0.9% saline and general surgical patients: a problem, not a solution. Ann Surg. 2012;255:830–2. [DOI] [PubMed]
138. Stephens R, Mythen M. Optimizing intraoperative fluid therapy. Curr Opin Anaesthesiol. 2003;16:385–92. [DOI] [PubMed]
139. Lee J. Plasma volume expanders and intraoperative fluid therapy. Korean J Anesthesiol. 2009;56:483–91. [DOI] [PubMed]
140. Bjerregaard LS, Møller-Sørensen H, Hansen KL, Ravn J, Nilsson JC. Using clinical parameters to guide fluid therapy in high-risk thoracic surgery. A retrospective, observational study. BMC Anesthesiol. 2015;15:91. [DOI] [PubMed] [PMC]
141. Langer T, Limuti R, Tommasino C, van Regenmortel N, Duval ELIM, Caironi P, et al. Intravenous fluid therapy for hospitalized and critically ill children: rationale, available drugs and possible side effects. Anaesthesiol Intensive Ther. 2018;50:49–58. [DOI] [PubMed]
142. Zawadzki B, Narciso RC, da Hora Passos R. Beyond the saline versus balanced debate: a neuro-systemic framework for fluid therapy in acute brain injury. Intensive Care Med. 2026;52:414–5. [DOI] [PubMed]