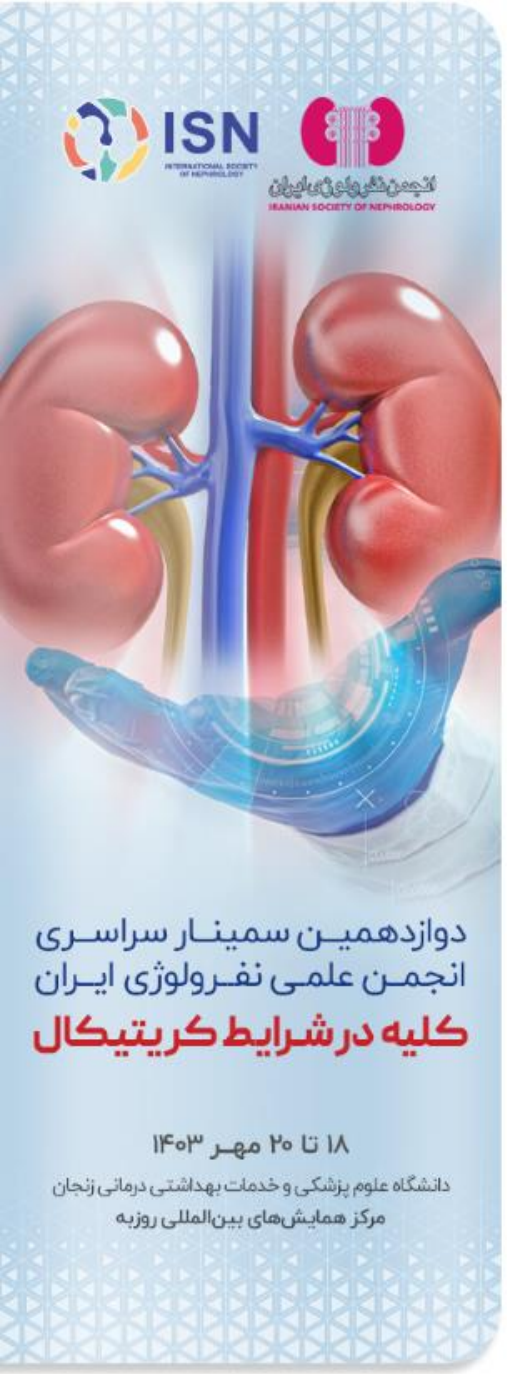

Chloride Disturbances in Critically Ill Patients

By:
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Chloride Balance

- Chloride is the major strong anion in blood, accounting for approximately:

1. one-third of plasma tonicity.
2. for 97 to 98% of all strong anionic charges.
3. for two-thirds of all negative charges in plasma.
4. Chloride is the predominant ECF ion with a normal concentration ranging from 96–111 meq/L.

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- The principal dietary chloride intake is in the form of salt and thus nutritional deficiencies of chloride are rare.
- Chloride and sodium have a significant role in maintaining:

1. Osmolarity
2. acid-base balance
3. electroneutrality of body fluids

- The various mechanisms and hormones that regulate sodium and volume balance also regulate chloride concentration, including the RAS system, sympathetic nervous system, ANP, and other factors affecting RBF.

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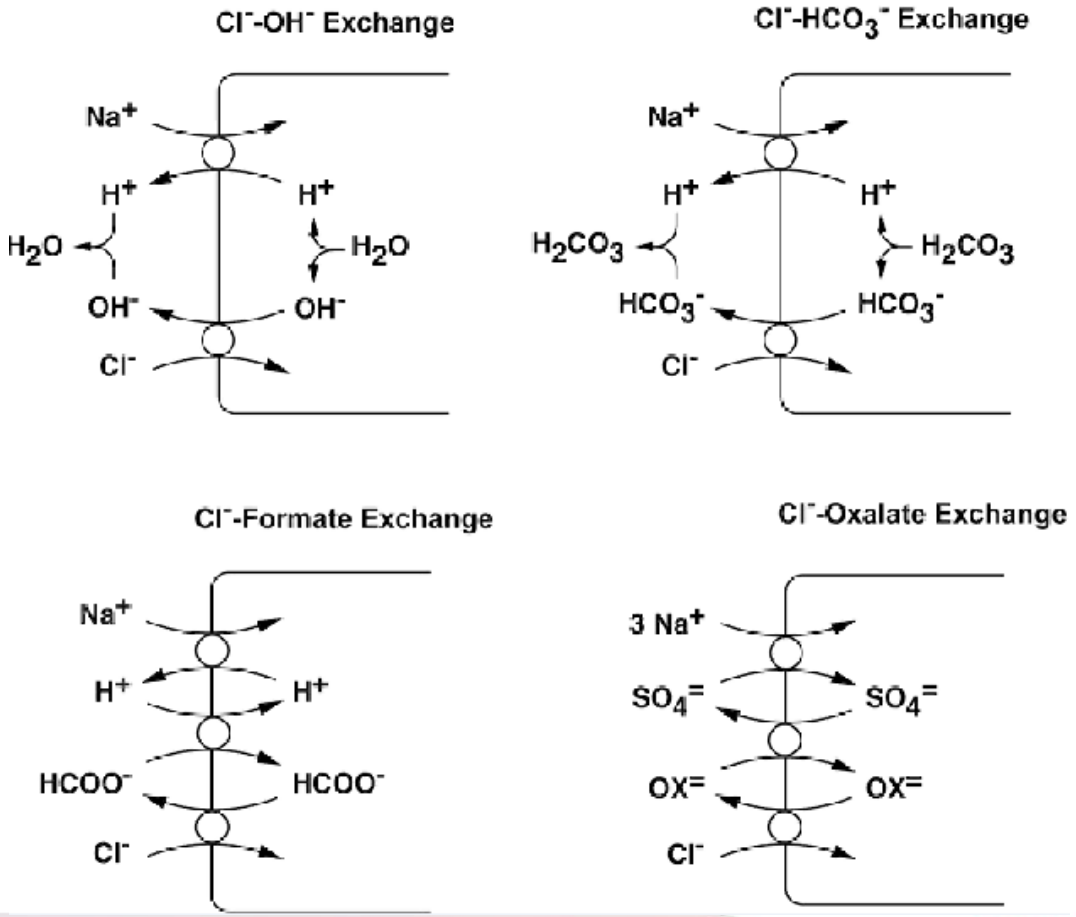
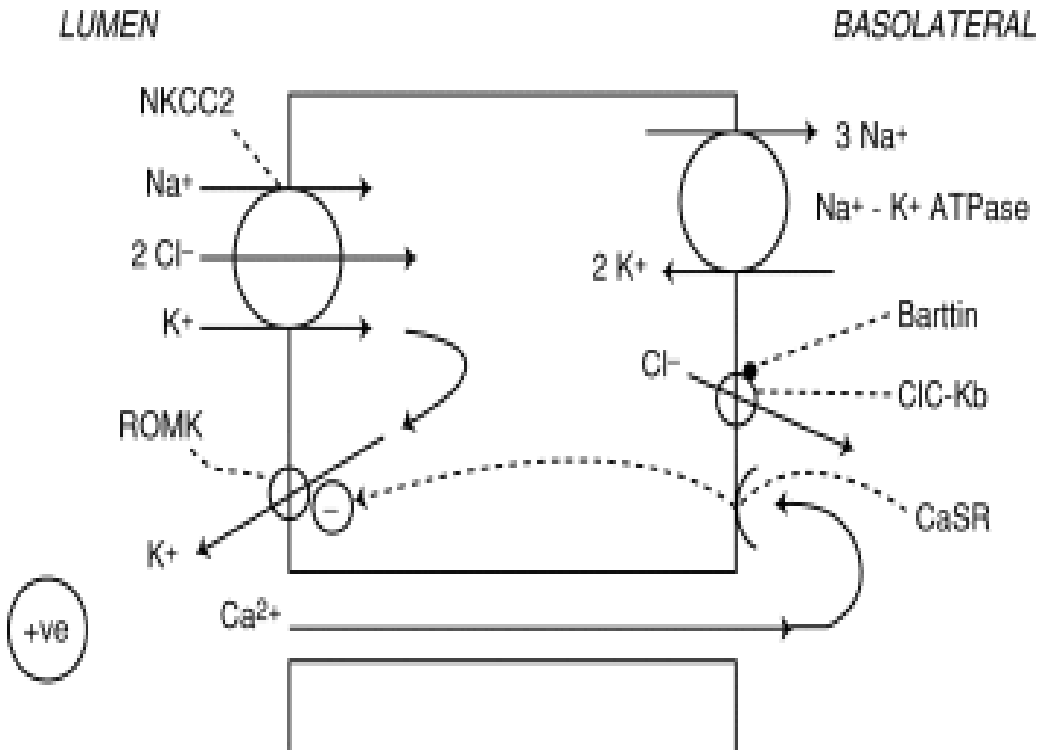
- Approximately 21,000 mEq of chloride is filtered everyday, of which >99% is absorbed and only 100–250 meq is excreted every day.
  Once in the proximal tubular lumen, chloride is reabsorbed actively via anion exchangers and on luminal side and leaves the cell via a K + Cl- co-transporter and chloride selective channels.(55%)



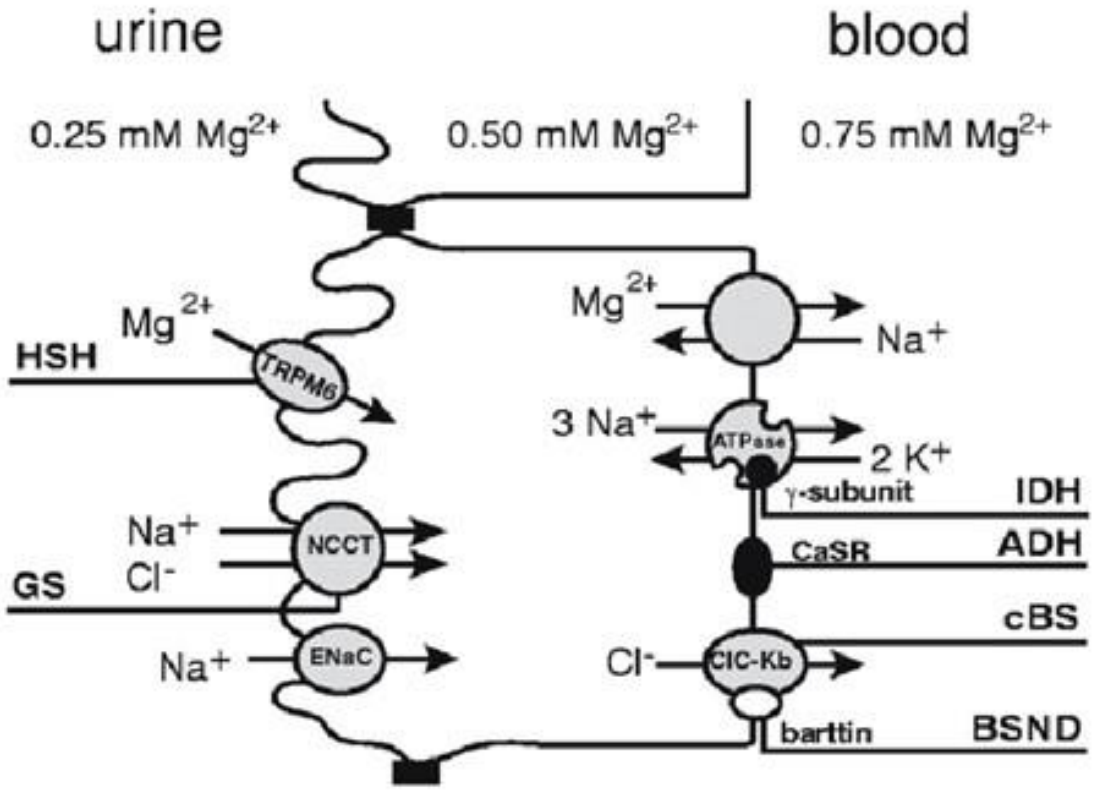
P. Anderson. 2007
CEFX in prevention of Hyperoxaluria and Urolithiasis.

- In the TAL, Chloride is reabsorbed via luminal Na-K-2Cl co-transporter and leaves the cell via ClC-Ka channel co-localized with Barttin protein. (25–35%)



Raymond Quigley MD, 2019
Renal aspects of Sodium metabolism in the Fetus and Neonate

- In the distal convoluted tubule, chloride is actively reabsorbed via luminal Na-Cl co- transporters and leaves the cell via basolateral chloride channels. (10-20%)



Bell PD, Feb 2003. Macula Densa Cell Signaling

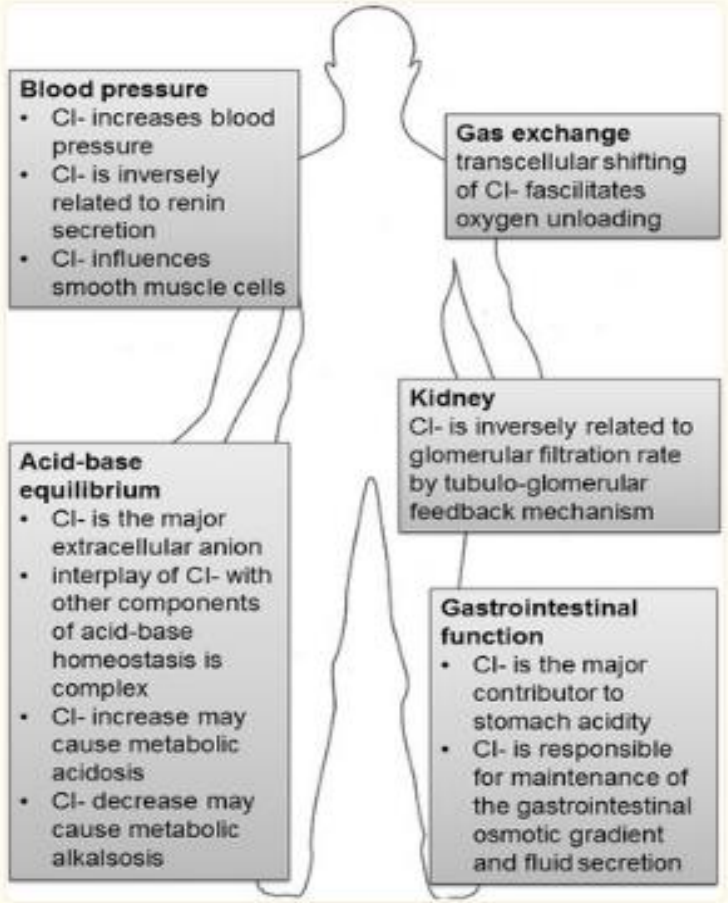


Fig. 1

The principal physiological functions of chloride in the human body

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- **Hypochloraemia: Serum Chloride≤ 96 mEq/L**

Table 1. Causes of hypochloremia.

Mechanism	Loss location	Example
Chloride loss	Gastrointestinal	Vomiting Gastric fluid drainage High-volume ileostomy drainage
	Renal	Diuretic use Bartter syndrome Gitelman syndrome
Excess water gain (compared with chloride)	Congestive heart failure Syndrome of inappropriate antidiuretic hormone	Infusion of hypotonic solutions
Excess sodium gain (compared with chloride)		Infusion of sodium bicarbonate

There usually aren't any symptoms or signs of hypochloremia. But there may be associated symptoms from underlying causes of hypochloremia.

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- **Hyperchloraemia: Serum Chloride≥111 mEq/L**

Table 2. Causes of hyperchloremia.

Mechanism	Loss location	Example
Chloride administration		Chloride-rich intravenous fluids
		Total parenteral nutrition
Water loss (true water loss or relative to chloride)	Renal	Diabetes insipidus
		Diuretic use
		Osmotic diuresis
		Postobstructive diuresis
	Extrarenal	Fever
		Hypermetabolic state
		Diarrhea
		Burns
		Exercise and severe dehydration
Definitive or relative increase in tubular chloride reabsorption		Renal tubular acidosis
		Renal failure
		Acetazolamide use
		Ureteral diversion procedure
		Post-hypocapnia

The clinical presentation is not specific for hyperchloremia; it depends on the underlying disease and hydration.

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Disorders of Chloraemia and Manipulation of Chloride in the ICU

- Hyperchloraemia or hypochloraemia, resulting from disease processes or clinical manipulations, is common in the ICU and should always be considered in relation to sodium.
- Chloride is also an essential component of intravenous fluids used in daily clinical practice and its concentration in different replacement. fluids (mmol/L) is as follows: 4% Albumin = 128; Normal saline (0.9%) = 154; Half normal saline (0.45%) = 77; Ringers lactate = 111,; PlasmaLyte = 98; Hydroxyethyl starch = 110–154.

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Composition of Crystalloid Solutions

Fluid	Sodium	Potassium	Calcium	Magnesium	Chloride	Acetate	Gluconate	Malate	Lactate	Osmolarity
Plasma	135–145	4.5–5.0	2.2–2.6	0.8–1.0	94–111	0.02–0.2			1–2	275–295
Plasma-Lyte A	140	5.0		3.0	98	27	23			294
Normosol-R	140	5.0		3.0	98	27	23			295
Isolyte S	141	5.0		3.0	98	27	23			295
Ringer's acetate	145	4.0	2.5	1.0	127	24		5		309
Lactated Ringer's	130	4.0	2.7		109				28	273
Hartmann's solution	131	5.4	1.8		112				28	280
0.9% sodium chloride	154				154					308

Am J Respir Crit Care Med. 2019 Apr 15; 199(8): 952–960.

- The commonest fluid used in clinical practice is normal saline.
- Unfortunately, the terminology itself is a misnomer as it is not normal because it has a higher sodium and chloride content relative to plasma and it is also slightly hyperosmolar.
- Intravenous administration of chloride-rich fluids is probably the most common and modifiable cause of hyperchloraemia in the ICU

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- Ringer’s lactate has less sodium and chloride content. However, the lactate that is present is converted into bicarbonate, and glucose is produced by the gluconeogenetic pathway.
- In patients with impaired hepatic function, lactic acidosis might occur and in diabetic patients, hyperglycemia is a possibility.
- Balanced salt solutions replace lactate with acetate and gluconate, which has an extrahepatic mechanism of conversion to bicarbonate.
- The level of acetate is too low to cause cardiovascular instability.

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The influence of Chloride on acid base homeostasis can be explained by the: "Stewart approach"

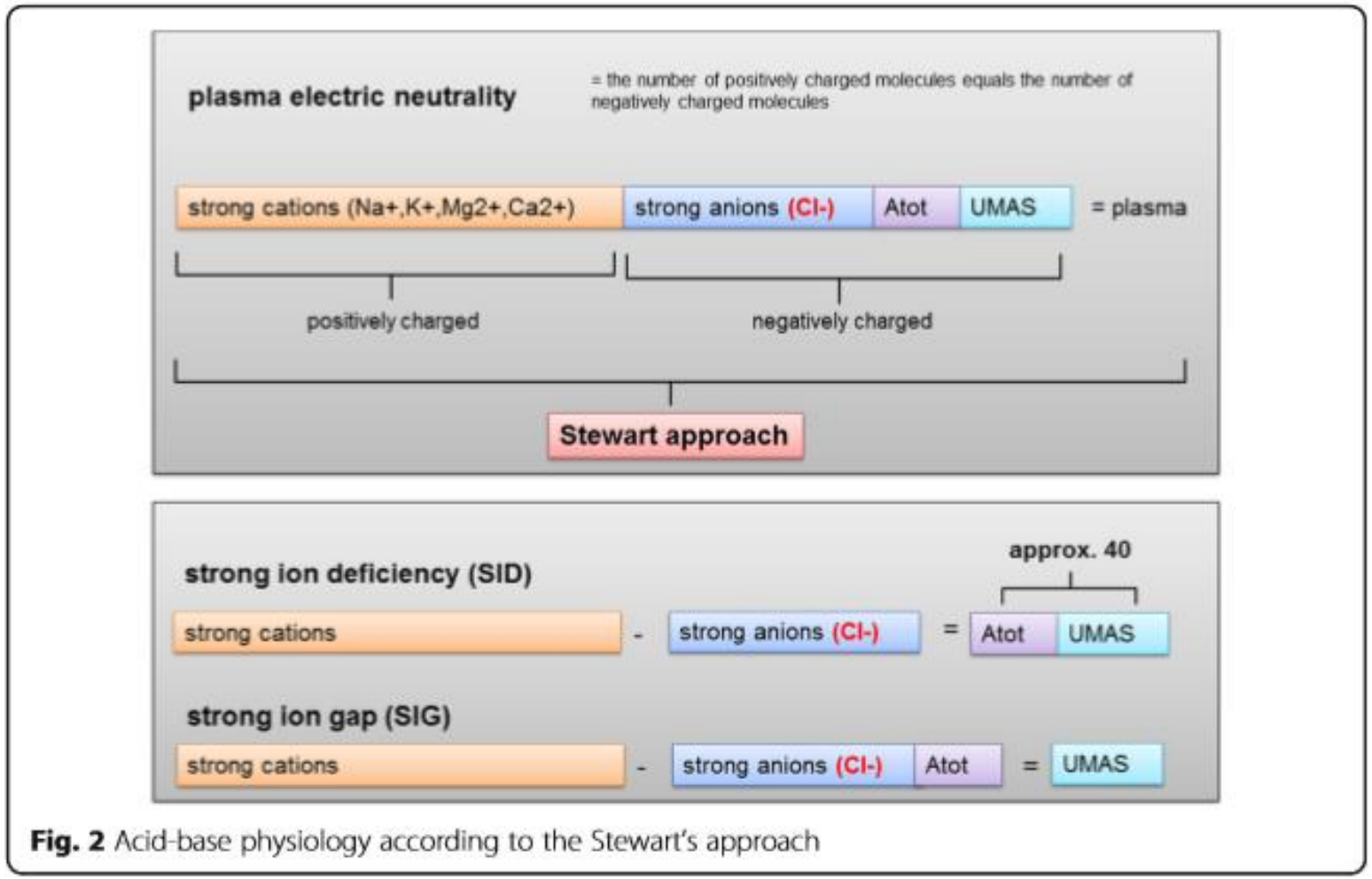

Fig. 2 Acid-base physiology according to the Stewart's approach

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- The SID of normal saline is 0, and as we know the lower the SID, the higher the possibility of metabolic acidosis. Thus normal saline has the propensity to cause metabolic acidosis.
- The SID of Ringer Lactate is 28.
- The SID of most of the balanced salt solutions exceeds 40; like the SID of Plasmalyte is 50.
- The alkaline state of the balanced salt solutions makes them a near ideal solution in metabolic acidosis.

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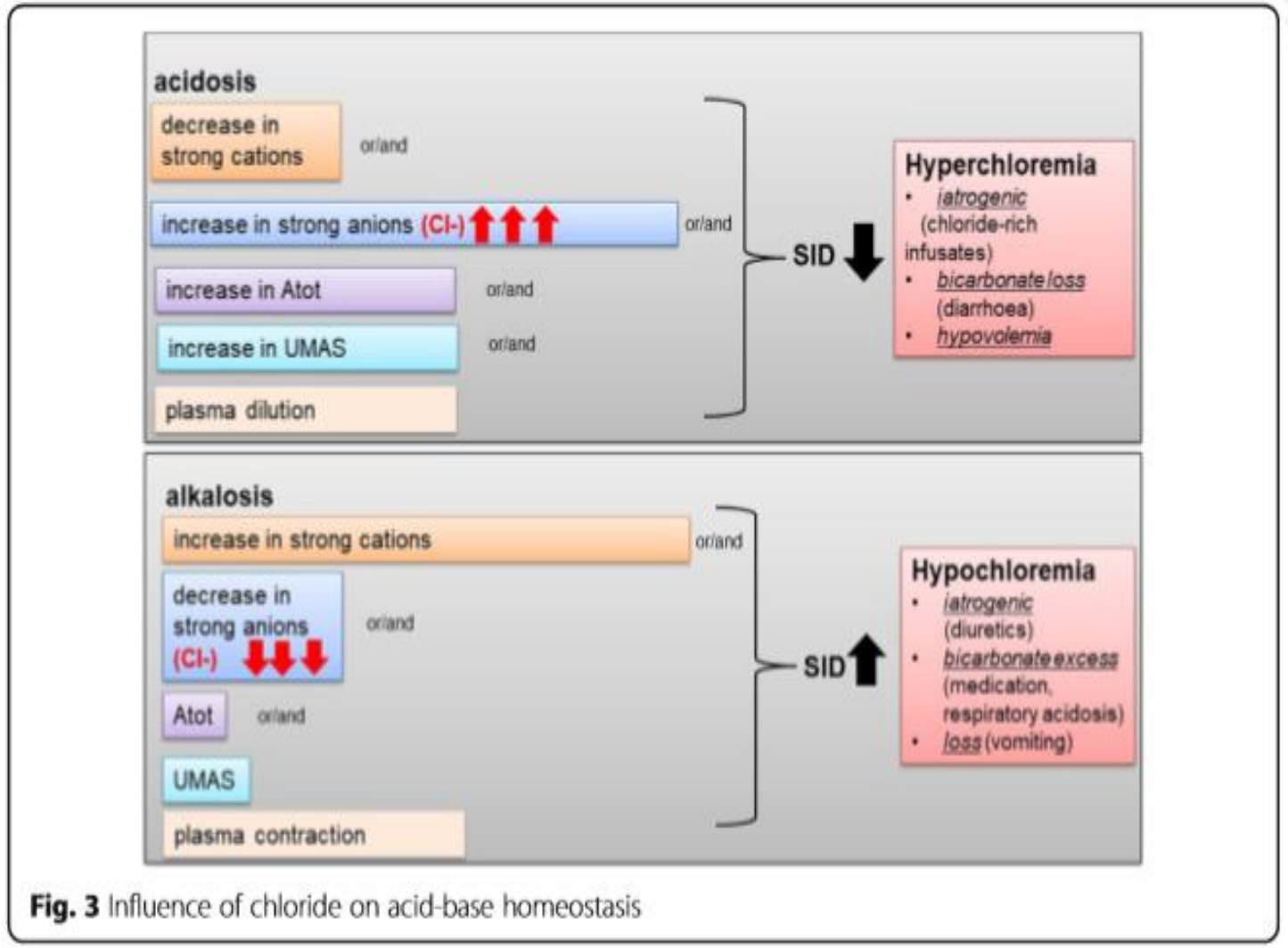

Fig. 3 Influence of chloride on acid-base homeostasis

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REVIEW

Chloride in intensive care units: a key electrolyte [version 1; referees: 3 approved]

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Abstract

Over the past few years, chloride has joined the league of essential electrolytes for critically ill patients. Dyschloremia can occur secondary to various etiologic factors before and during patient admission in the intensive care unit. Some cases are disease-related; others, treatment-related. Chloride abnormalities were shown in animal models to have adverse effects on arterial blood pressure, renal blood flow, and inflammatory markers, which have led to several clinical investigations. Hyperchloremia was studied in several settings and correlated to different outcomes, including death and acute kidney injury. Baseline hypochloremia, to a much lesser extent, has been studied and associated with similar outcomes. The chloride content of resuscitation fluids was also a subject of clinicall research. In this review, we describe the effect of dyschloremia on outcomes in critically ill patients. We review the major studies assessing the chloride content of resuscitation fluids in the critically ill patient.

Open Peer Review

Referee Status: ✓ ✓ ✓

	Invited Referees 1	2	3
version 1 published 01 Nov 2017	✓	✓	✓

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Dyschloremia in the ICU

- The reported prevalence of hypochloremia has varied according to the clinical setting and patient population.
- In the general ICU setting, different studies have reported an incidence between 6.7% and 37%. Among patients with heart failure, the reported incidence varied from 13% to 23%.

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- Hyperchloremia is common in critically sick patients, with evidence indicating that it may occur in between 25%–45% of ICU patients;
- It occurs in around 75% of ICU patients within the initial 24 hours of their hospitalization.

The Egyptian Journal of Hospital Medicine (January 2022) Vol. 86, Page 532-537

Associations of dyschloremia and outcomes in the ICU

- Tani and colleagues reported the association of hypochloremia with increased ICU length of stay and death in a mixed surgical and medical ICU setting.

Tani M: The incidence and prognostic value of hypochloremia in critically ill patients. ScientificWorldJournal. 2012

- In another report, Kimura and colleagues found that hypochloremia within the first 48 hours postoperatively was independently associated with an increased mortality rate compared with patients who had normal chloride levels, even after adjustment for illness severity.

Kimura S, Matsumoto S, Muto N, et al.: Association of serum chloride concentration with outcomes in postoperative critically ill patients: a retrospective observational study. J Intensive Care. 2014; 2(1): 39

- Shao and colleagues reported in a cohort study, the incidence of hypochloremia before ICU admission was high and reported as 37%.
- They found that baseline hypochloremia and hyperchloremia were independent risk factors for the development of AKI compared with normochloremia.
- They also noted longer ICU and hospital lengths of stay as well as increased mortality rate in the presence of hypochloremia.

Shao M, et al.: Dyschloremia Is a Risk Factor for the Development of Acute Kidney Injury in Critically Ill Patients. PLoS One. 2016; 11(8): e0160322

- In another study, authors demonstrated an association between hypochloremia and longer use of non-invasive ventilation in patients with exacerbation of COPD.
- Not only hypochloremia but the rate of increase in chloride level has been found to be associated with worse outcomes among hospitalized patients.

Terzano C, Di Stefano F, Conti V, et al.: Mixed acid-base disorders, hydroelectrolyte imbalance and lactate production in hypercapnic respiratory failure: the role of noninvasive ventilation. PLoS One. 2012; 7(4): e35245.

- Neyra and colleagues found that, among hyperchloremic patients with severe sepsis or septic shock, a higher chloride level at 72 hours after ICU admission was associated with a higher mortality rate.
- They also noted an increase in death (odds ratio of 1.37) with each 5 mEq/L increase in chloride level among those patients. Interestingly, they did not find a relationship between ICU admission chloride level and death.

Neyra JA, Canepa-Escaro F, Li X, et al.: Association of Hyperchloremia With Hospital Mortality in Critically Ill Septic Patients. Crit Care Med. 2015; 43(9): 1938–44.

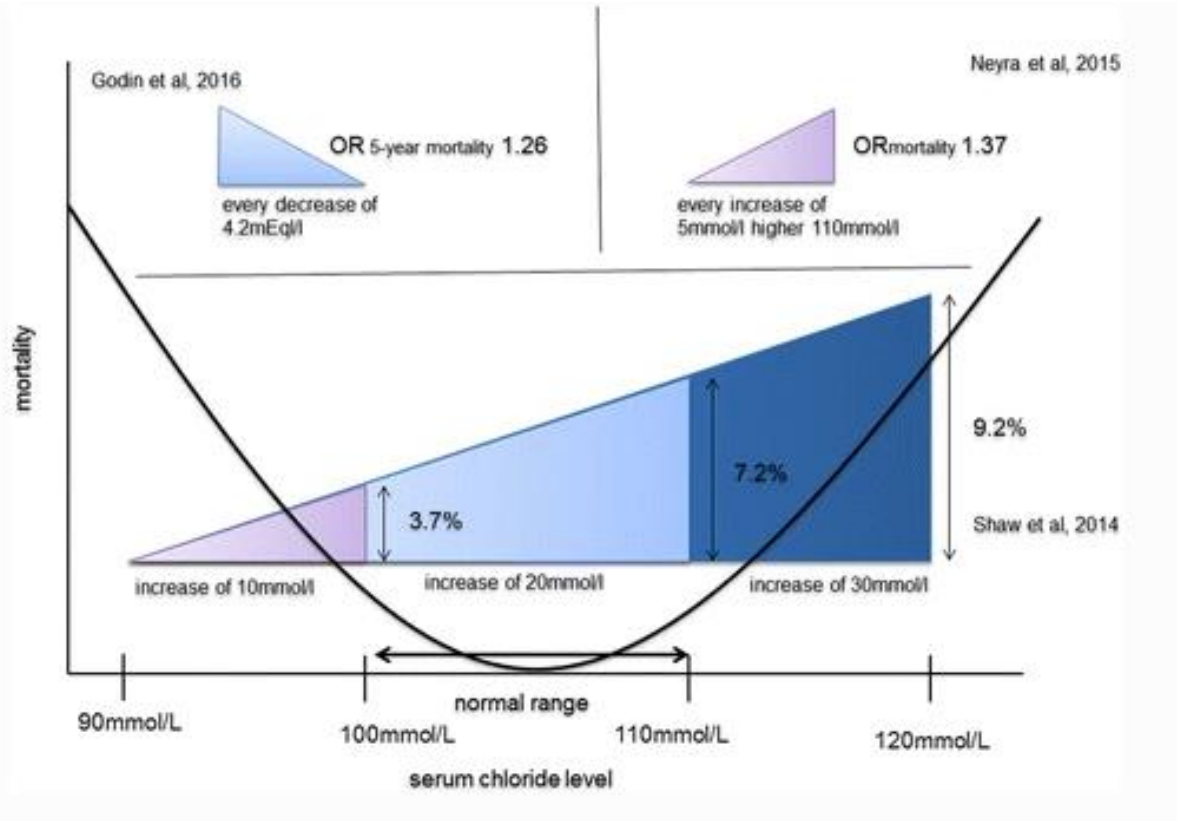
- In trauma patients, hyperchloremia 48 hours after ICU admission and a change in chloride levels were independent predictive factors of the 30-day mortality rate.

Lee JY, Hong TH, Lee KW, et al.: Hyperchloremia is associated with 30-day mortality in major trauma patients: a retrospective observational study. Scand J Trauma Resusc Emerg Med. 2016; 24(1): 117.

- In a study, after non-cardiac surgery, for patients with normal preoperative serum chloride level, death was associated with postoperative hyperchloremia, and in a mixed ICU population, higher mortality rates were associated with ICU admission hyperchloremia though not with patients undergoing elective cardiac surgery.

McCluskey SA, Karkouti K, Wijeysundera D, et al.: Hyperchloremia after noncardiac surgery is independently associated with increased morbidity and mortality: a propensity-matched cohort study. Anesth Analg. 2013; 117(2): 412–21.

Influence of chloride levels on mortality



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- Following the examination of the body of literature about the consequences of chloride-rich versus more balanced solutions on critically ill patients, It is noted that earlier studies suggested that the use of balanced fluids may be associated with less AKI and need for RRT.

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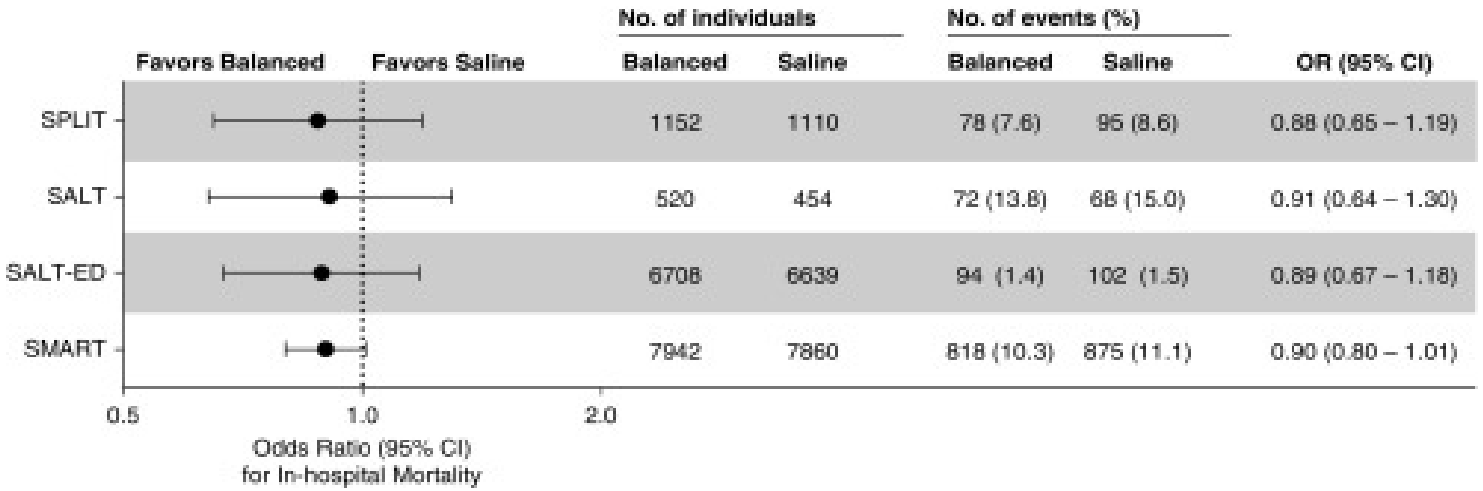

	No. of individuals		No. of events (%)		
	Balanced	Saline	Balanced	Saline	OR (95% CI)
SPLIT	1152	1110	78 (7.6)	95 (8.6)	0.88 (0.65 – 1.19)
SALT	520	454	72 (13.8)	68 (15.0)	0.91 (0.64 – 1.30)
SALT-ED	6708	6639	94 (1.4)	102 (1.5)	0.89 (0.67 – 1.18)
SMART	7942	7860	818 (10.3)	875 (11.1)	0.90 (0.80 – 1.01)

Am J Respir Crit Care Med. 2019 Apr 15; 199(8): 952–960.

Conclusion

- Chloride has been neglected for too long. Alterations in the chloride balance and chloraemia, both absolute and relative to natremia, can alter the acid–base status, cell biology, renal function, and haemostasis but the clinical consequences of these biological and physiological alterations remain unclear.
- Most of these alterations appear to have negative implications so there is an urgent need to conduct trials & research into the epidemiology and outcome implications of disorders of chloride balance and chloride concentration.

F1000Research 2017, 6(F1000 Faculty Rev):1930 Last updated: 02 NOV 2017