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Dyschloremia In the Surgical Resuscitation and Post-Anesthesia Care Unit

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Abstract

Introduction: *Dyschloremia are common electrolyte imbalances that especially affect the critically ill patients. There has been an increasing interest in chloride variations in the recent years*

Methods and material: *The present work is a retrospective study conducted at the surgical resuscitation and post-anesthesia care unit (P17) at the Ibn Rochd University Hospital of Casablanca. This study involved 209 patients during a span of 2 years.*

Results: *Our study showed a male predominance and sex ratio of 1.52 with an average age of our patients was 42.53 years. The main reasons for hospitalization were polytrauma, followed by head trauma and stroke. The main clinical signs observed in our patients were dominated by an altered mental status (GCS< 12), hypotension, tachycardia and hypothermia. Biologically, 49.3% of the patients had dyschloremia on admission, while 50.7% of patients had hospital acquired dyschloremia. During hospitalization, 57% of these patients acquired dyschloremia on the 2nd day of hospitalization.*

The most common form of dyschloremia was hypochloremia with a percentage of 85.2%. Natremia and Kalemia were disturbed in 34.92% and 55.98% of cases respectively.

Other disturbances of the haemogram and haemostasis were noted such as hyperleukocytosis, thrombocytosis, low prothrombin rate and prolonged activated partial thromboplastin time.

Regarding the therapeutic procedures undertaken on admission, 61% of patients received vascular filling with 0.9% saline. Vasoactive drugs and diuretics were used in 24.9% and 11.5% of cases respectively. 67.34% of our patients required transfusion; red blood cell concentrates constituted 76.8% of the total quantity of labile blood products used.

The average length of hospitalization of patients with dyschloremia was 9.64 days and their evolution was favorable in 71.77% of cases.

In our series, the most common types of complications were neurological, digestive, renal, hemodynamic and cardiac (irregular rhythm).

Conclusion: *In literature, fluctuations in blood chloride concentrations were a risk factor for excess mortality and morbidity in critically ill patients. To date, the literature emphasizes the role of unbalanced saline solutions in the induction of acquired hyperchloremia, which is responsible for numerous organic complications, as well as the interest in using balanced solutions in the case of large volume infusions.*

Keywords: *Hyperchloremia, hypochloremia, electrolyte imbalances, surgical resuscitation, post-anesthesia care, mortality.*

Introduction

Chloride is a major anion in the body, involved in numerous physiological functions (regulation ofcell volume, immune function, regulation of acid-base metabolism, production of hydrochloric acid in the stomach). It is also the main anion in the blood ionogram, with concentrations ranging from 95 to 105 mEq/L. Chloride ensures electrolyte balance (equal concentration of anions and cations). In the vast majority of cases, blood chloride levels follow changes in blood sodium concentration (natremia).

To date, several studies have highlighted the fact that hyperchloremia induces renal, digestive [5], cerebral and coagulopathic complications and is directly correlated to an excess in morbidityand mortality in intensive care patients [1]. Hyperchloremia is also responsible for the occurrence of hyperchloremic metabolic acidosis both intraoperatively and in the post-anesthesia care unit [6,7].

Numerous data underline the impact of hyperchloremia on immunity: hyperactivation of the immune system via its cellular and humoral pathways, responsible for the release of pro-inflammatory mediators and immune cells independently of pH variations [1,2].

In contrast, hypochloremia was proven to be directly linked

to an increase in the mortality of patients with coronary disease [6], heart disease [1], kidney disease [4], liver disease [5] andbrain trauma [2].

The aim of our work is to describe the epidemiology, clinical characteristics, therapeutic meansand evolution of patients managed for dyschloremia in the surgical resuscitation and post-anesthesia care unit.

Materials and Methods

1. Type of study and context:

This is a retrospective descriptive study based on the exploitation of records of patients hospitalized in the surgical resuscitation and post-anesthesia care unit (P17) at the Ibn RochdUniversity Hospital of Casablanca.

Our study involved 209 patients with dyschloremia, over a 2-year period (2018-2019).

Data were collected using a pre-established operating form detailed in Appendix 1, it included:

- Age
- Gender
- Medical and surgical history
- Length of hospital stay
- Diagnosis
- Clinical data
- Paraclinical data
- Proposed treatment
- Evolution

2. Sampling

In this study, 209 complete files were considered and included in the study.

- Inclusion criteria:

We included in the study all patients who presented with dyschloremia on admission or duringhospitalization.

- Exclusion criteria:

We excluded from the study patients with no sign of dyschloremia and also incomplete records.

3. Data analysis

Initial data entry was done on Microsoft Excel and statistical analysis was performed usingSPSS V21 software.

Descriptive results were represented as headcounts and percentages for qualitative variables, and measures of central tendency and dispersion (mean, median, standard deviation) were used for quantitative variables. These indicators (percentage, mean, median, standard deviation) were defined for each item on the data sheet, and the "Evolution" parameter was correlated with the characteristics of dyschloremia in our patients.

The analysis carried out during this study focused on several points, namely:

- Frequency of dyschloremia during the study period
- Epidemiological data on patients: age, sex and terrain
- Medical and surgical history
- Reason for hospitalization
- Clinical and paraclinical data
- Assessment of dyschloremia
- Treatment
- Length of stay and evolution

Results

1. Demographic and anamnestic data

A. Age:

In our study, patient ages ranged from 15 to 79 years, with an average of 42.53 (± 18) years.The over-55 age group accounted for 26.3% (55 cases) of all patients, while only 28 patients(13.4%) were aged between 35 and 45 (Figure 1).

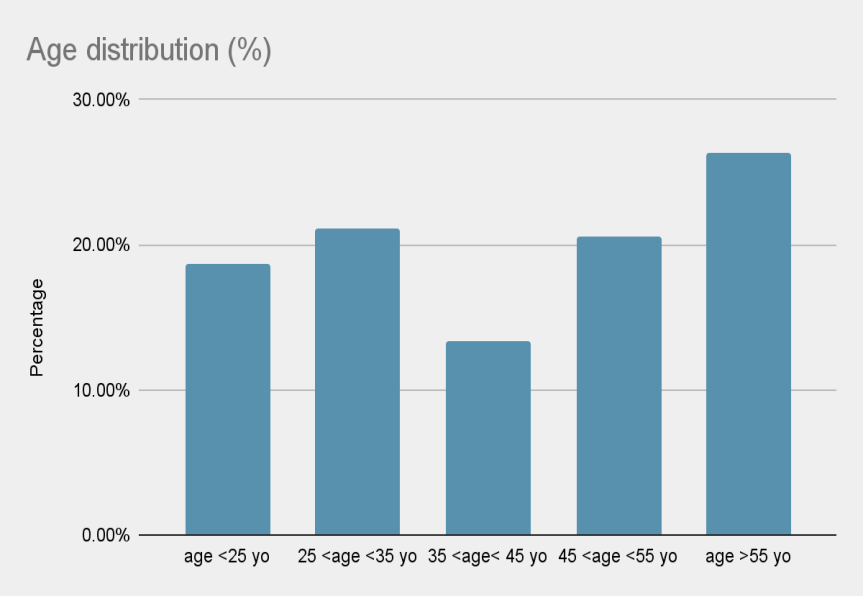

Figure 1: Age distribution.

B. Gender

Of a total of 209 patients, 127 (60.8%) were predominantly male. The M/F sex ratio was 1.52.This distribution is shown in Figure 2.

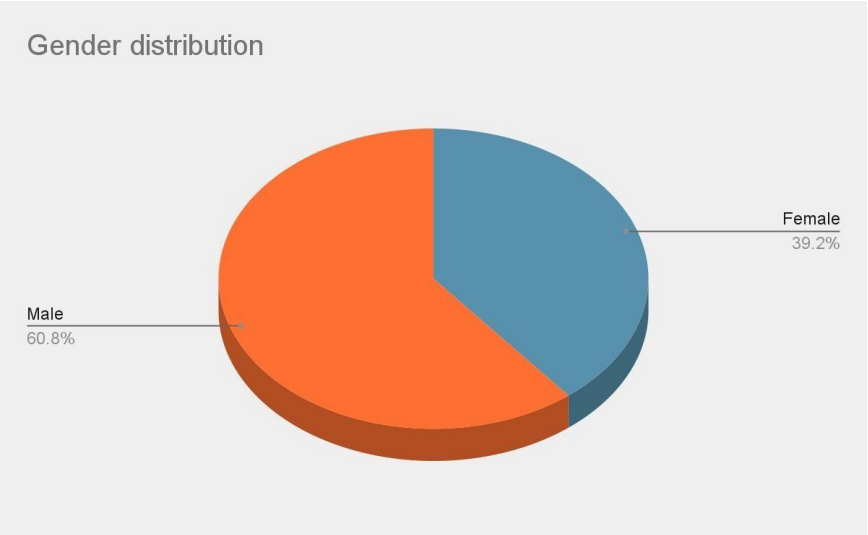

Figure 2: Gender distribution.

C. Reason for stay

Polytrauma was the most frequent reason for hospitalization in our series, with 63 cases (33%). Severe head trauma accounted for 33 cases (16%), while stroke and bowel obstruction togetherwere involved in only 27 cases (13%).

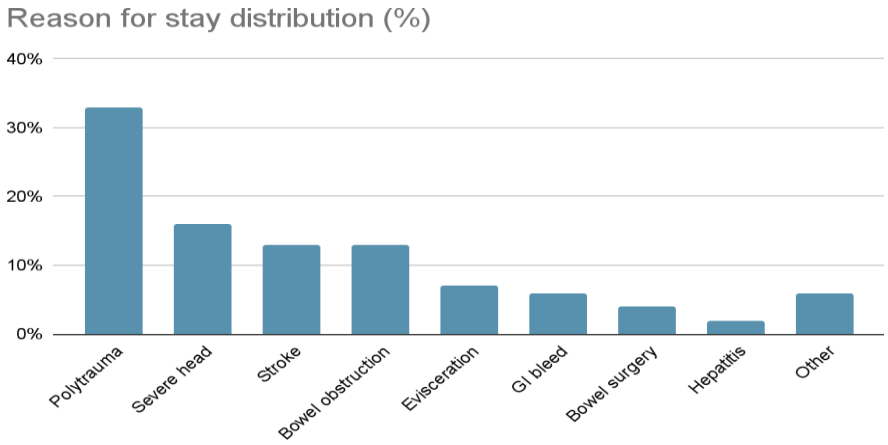

Figure 3: Reason for stay distribution.

D. Medical and surgical history

Patient history was divided as follows:

- Medical history : 47 patients (i.e. 22.5%) were diabetic, 36 patients (i.e. 17.2%) had hypertension, 11 patients (i.e. 5.3%) had heart failure, 10 patients (i.e. 4.8%) were asthmatic, 29 patients (i.e. 13.9%) werecirrhotic, 40 patients (i.e. 19.1%) had chronic vomiting and 11 patients (i.e. 5.3%) had cancer.

History	Disease	%
	Diabetes	22.5%
	Chronic vomiting	19.1%
	High blood pressure	17.2%
Medical history	Liver cirrhosis	13.9%
	Cancer	5.3%
	Heart failure	5.3%
	Asthme	4.8%

Table 1: Disease distribution.

- **Surgical history:** In our study, 21 patients (i.e. 10%) had undergone previous surgery.
- **Addictions and substance abuse:** In our study, 17 patients (i.e. 8.1%) were chronic smokers and 9 patients (i.e. 4.3%) werealcoholics.

History	Disease	%
Addictions and substanceabuse	Tobacco	8.1%
	Alcohol	4.3%

Table 2: Addictions and substance abuse distribution.

4. Clinical findings

In our series, the main clinical signs observed in our patients were as follows:

- **Heart rate:** Heart rate was abnormal in 179 patients (85.6%).
- Temperature: Fever was noted in 113 patients (54.1%).
- **Blood pressure:** Blood pressure was abnormal in 184 patients (88%).
- **Respiratory frequency:** Respiratory rate was abnormal in 57 patients (27.3%).
- **Glasgow coma score:** According to the Glasgow score analysis, 146 patients (70%) had a score below normal (below 15).

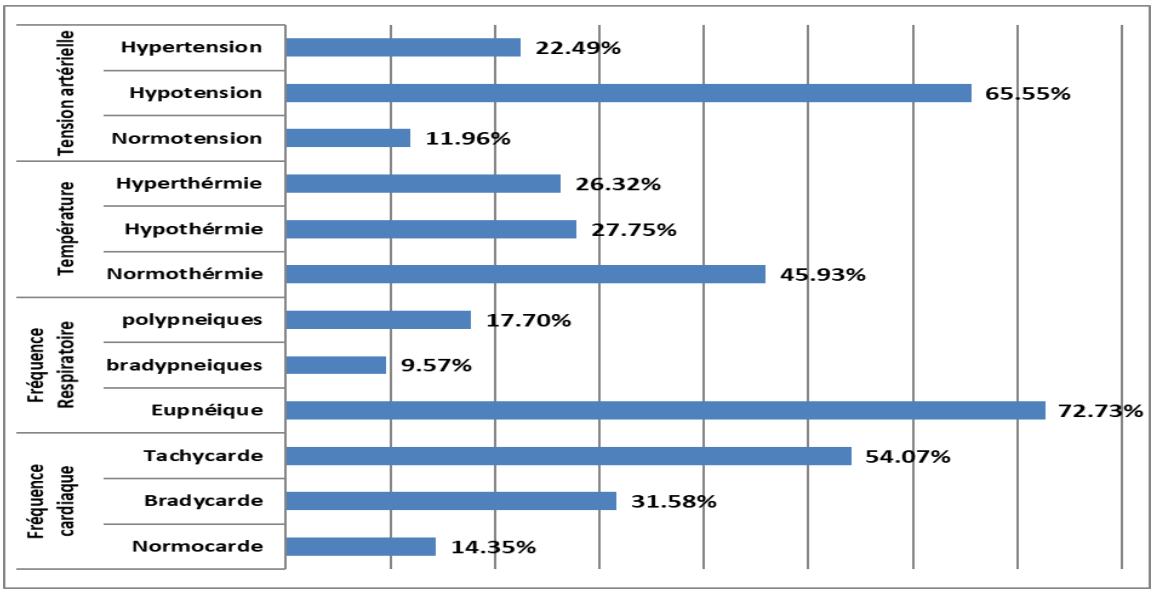

Figure 5: Vitals distribution.

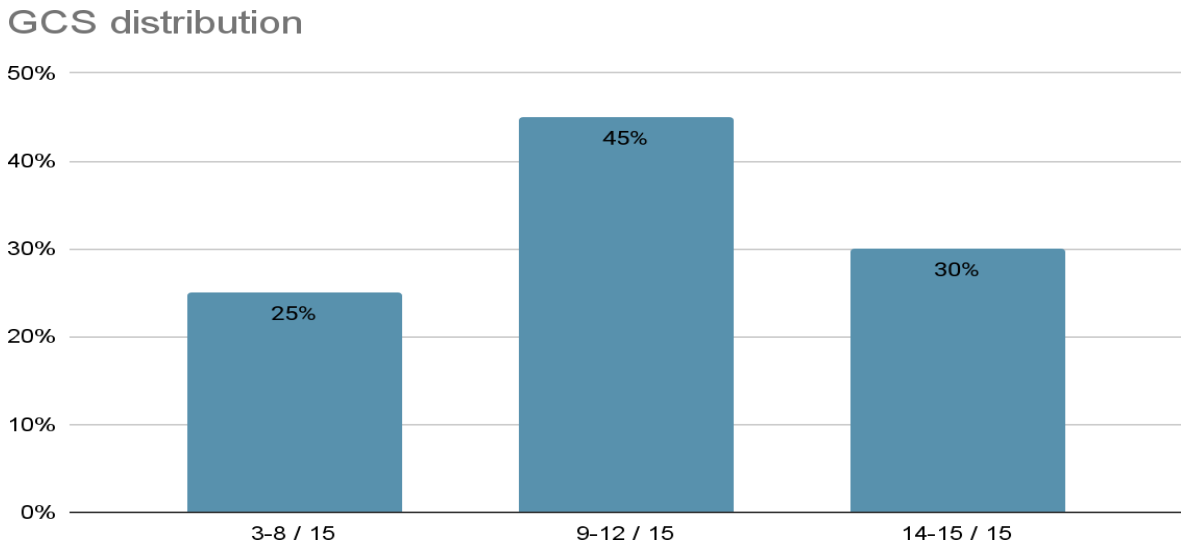

Figure 6: Glasgow Coma Scale distribution.

5. Paraclinical findings: biology

A. Blood count (CBC):

- **Red blood cell abnormalities:** According to the blood count study ,103 patients (i.e.49.32%) had an abnormal blood count, ofwhom 100 patients (i.e. 43.54%) had anemia and 12 patients (i.e. 5.78%) had polycythemia.
- **White blood cell abnormalities:** According to the blood count study, 49 patients (i.e. 23.81%) had an abnormal white blood cellcount, of whom 6 patients (i.e. 2.76%) had leukopenia and 44 patients (i.e. 21.05%) had hyperleukocytosis.
- **Platelet abnormalities:** According to our study, 85 patients (i.e. 40.7%) had abnormal platelet levels, of whom 23 patients (i.e. 11.4%) had thrombocytopenia and 40 patients (i.e. 19.42%) had thrombocytosis.

B. Fluid and electrolyte balance:

- **Chloride:** In our study ,103 patients (i.e. 49.3%) had dyschloremia on admission and 106 patients (i.e. 50.7%) acquired it during hospitalization. 57 patients (27.27%) acquired dyschloremia on the 2nd day of hospitalization, and 17 patients (8.13%) acquired it on the 3rd day of hospitalization.In addition, we observed hypochloremia in 178 patients, with a percentage of 85.2%.

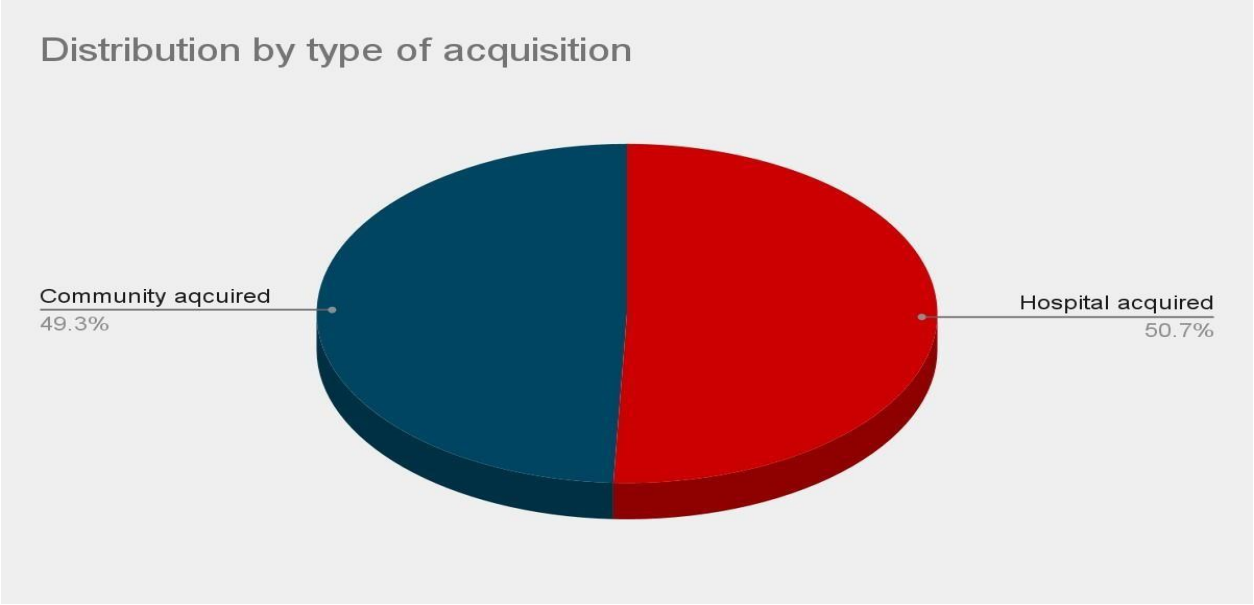

Figure 8: Breakdown by type of acquired dyschloremia.

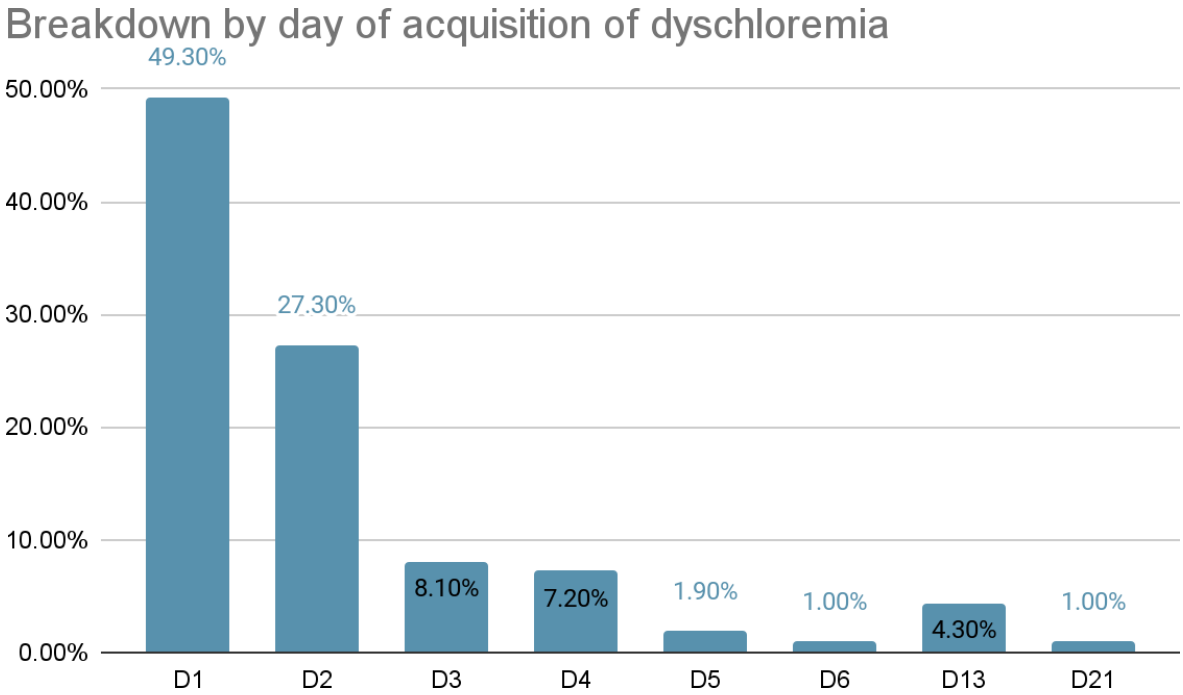

Figure 9: Breakdown by day of acquisition of dyschloremia.

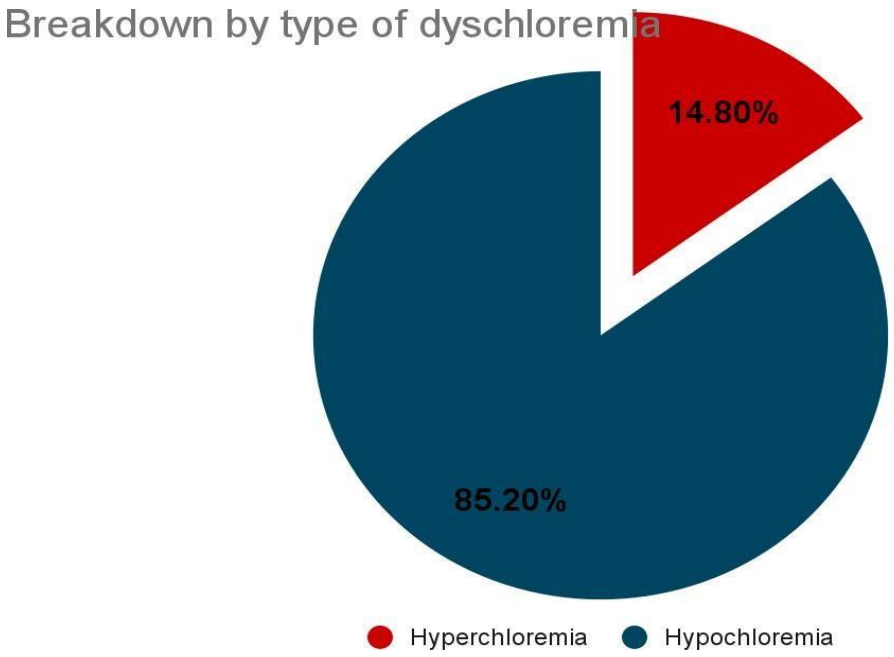

Figure 10: Breakdown by type of dyschloremia.

- **Sodium and potassium:** In our study, dysnatremia was noted in 73 patients (i.e. 34.92%) with hyponatremia in 69 patients (i.e. 33.01%) and hypernatremia in 4 patients (i.e. 1.91%).

Dyskalemia was noted in 117 patients (55.98%), with hypokalemia in 102 patients (48.80%) andhyperkalemia in 15 patients (7.18%).

Metabolite	Disease	n	%
	Normal	136	65.07%
Sodium	Hyponatremia	69	33.01%
	Hypernatremia	4	1.91%
	Normal	92	44.02%
Potassium	Hypokalemia	102	48.80%
	Hyperkalemia	15	7.18%

Table 3: Sodium and potassium anomalies breakdown.

A. **C-reactive protein:** CRP was requested in 43 patients (21%), and showed elevated levels in all cases, ranging from70 mg/l to 172 mg/l.
B. **Renal work-up:** Renal tests were carried out on 186 patients (89%), revealing renal failure in 31 patients (14.83%).
C. **Haemostasis:** Low prothrombin levels (PT) were found in 96 patients (46%). The latter was below 50% in 23 patients (11.11%). On the other hand, a prolonged activated partial thromboplastin time (APTT)was found in 66 patients (32%).

6. Proposed treatment

- Vasoactive drugs: Vasoactive drugs were used in 52 patients (24.9%).
- Diuretics: Diuretics were used in 24 patients (11.5%).
- Vascular filling: In our series, vascular filling was undertaken in 127 patients (61%), mainly with 0.9% salinesolutions.
- Blood transfusion: In our study 140 patients (67.34%) required blood transfusion.

The blood derivatives used for transfusions were: Red cell concentrate (RBC), fresh frozenplasma (FFP) and platelet concentrate (PC).

Red blood cell concentrates accounted for 76.8% of the total quantity of labile blood products used, followed by fresh frozen plasma (8.1%) and platelet concentrates in 1.3% of cases. With transfusions comprising two or three labile blood products (LBS): RBC+FFP in 9.4% of cases;RBC+PC in 1.3% of cases and RBC+FFP+PC in 3.1% of cases.

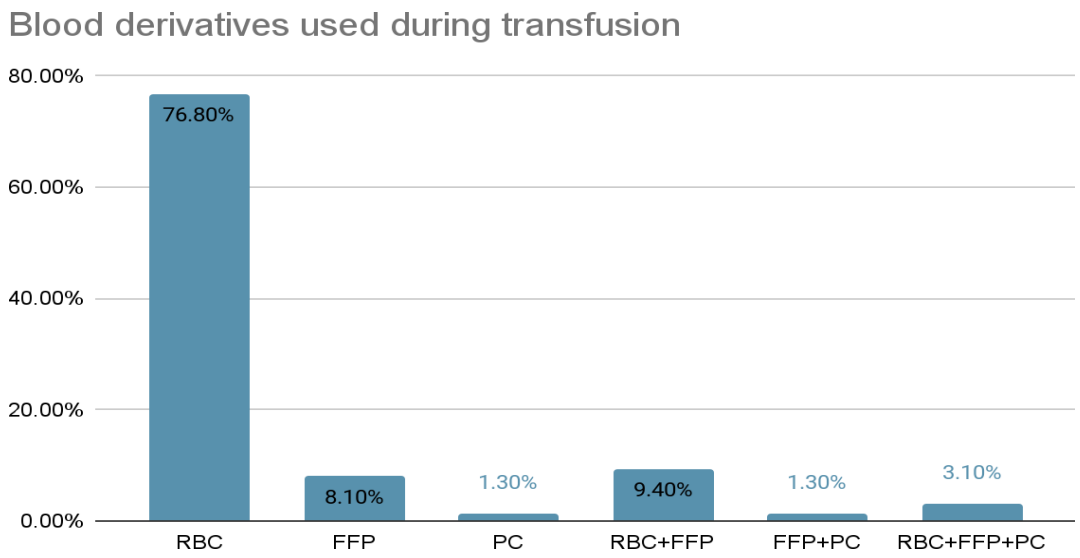

Figure 11: Blood derivatives used during transfusion.

7. Evolution:

A. Length of hospital stay: The mean length of hospitalization for patients with dyschloremia was 9.64 days, with extremes ranging from 1 to 36 days.

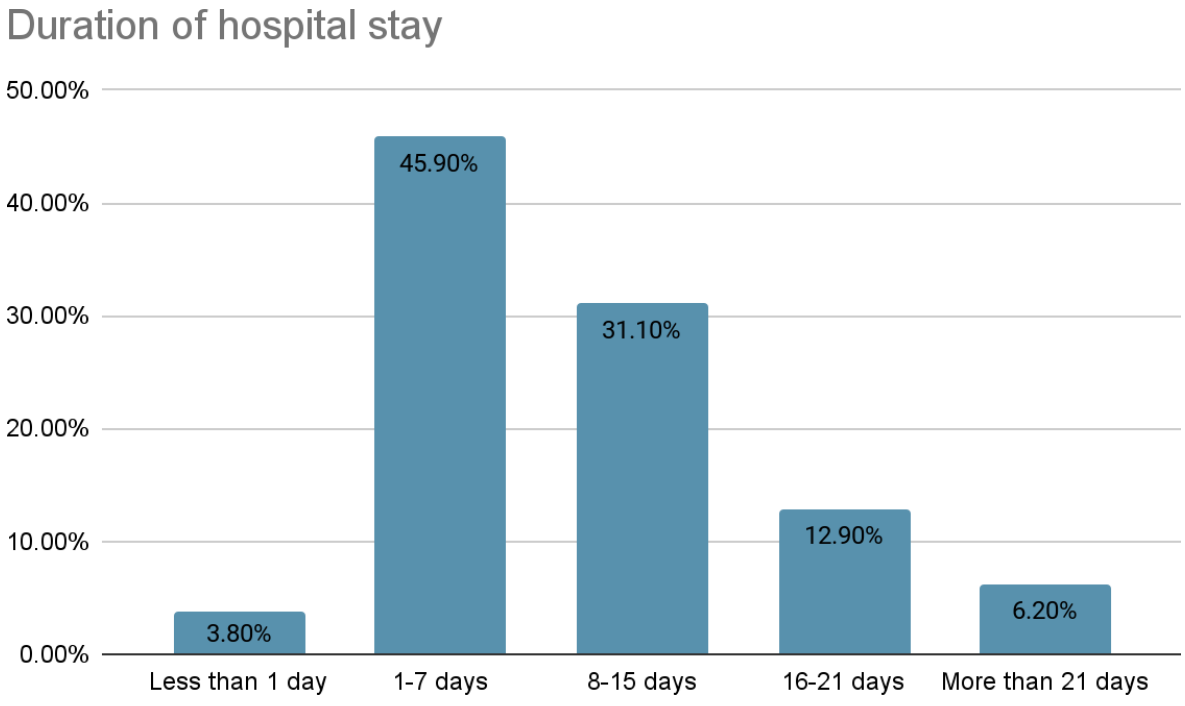

Figure 12: Breakdown by duration of stay.

A. Complications: In our series, 50 cases (23.92% of patients) had a complication.

- Digestive complications: Stomatitis was the most frequent with a rate of 25% followed by digestive hemorrhage in 12% ofcases and fistulae in 3%.
- Neurological complications: Neurological aggravation was noted in 50% of patients. Seizures were reported in 4% of patients, intracranial hypertension in 8% and coma in 21%.
- Cardiocirculatory complications: Rhythm disorders were noted in 17% of patients, collapse was found in 27% of patients.
- Others: Renal failure was noted in 27% of patients, and acute lung edema was noted in 2%.

Metabolite	Disease	%
	GCS alteration	50%
Neurological complications	Coma	21%
	Seizure	8%
	Other	17%
Cardio-vascularcomplications	Heart rhythm disorder	17%
	cardio-vascular collapse	27%
	Stomatitis	25%
Digestive complications	GI bleed	12%
	Fistulae	3%
	Acute renal injury	27%
Other complications	Acute pulmonary edema	2%

Table 4: Types of complications breakdown.

A. Mortality: Progression was assessed clinically (temperature, hemodynamic and respiratory status, consciousness), biologically (CBC, blood gas, CRP, renal function, BBB). The outcome wasfavorable in 150 patients (71.77%).

- Mortality according to blood chloride level (hyperchloremia-hypochloremia): In our study, 59 patients (28.23%) died. The death rate in patients with hyperchloremia was high in 27 (87.02%), while the death rate inpatients with hypochloremia was low in 32 (17.98%).

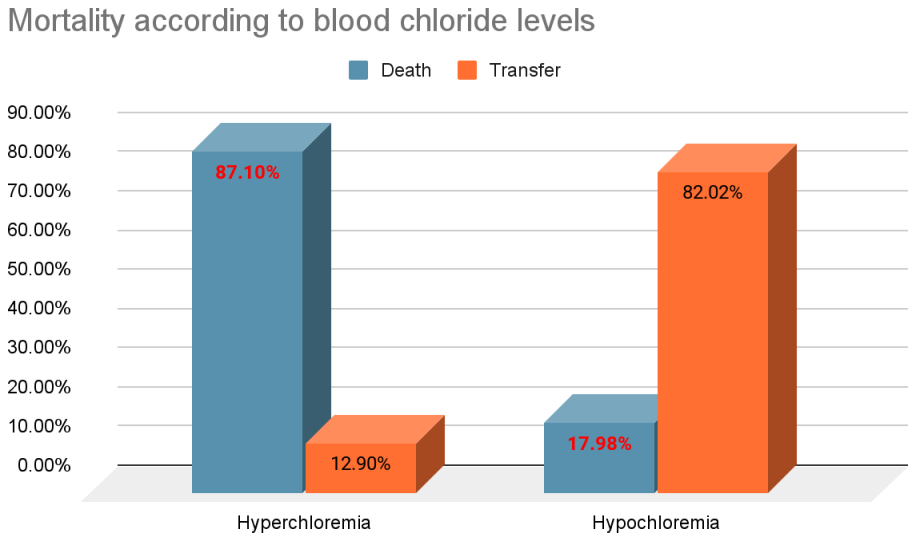

Figure 13: Mortality according to blood chloride levels.

- Mortality according to type of dyschloremia (community acquired or hospitalacquired): We observed that the mortality rate among patients with dyschloremia on admission (29.13%)was slightly higher than that found among patients who acquired dyschloremia during their hospitalizations (27.36%).

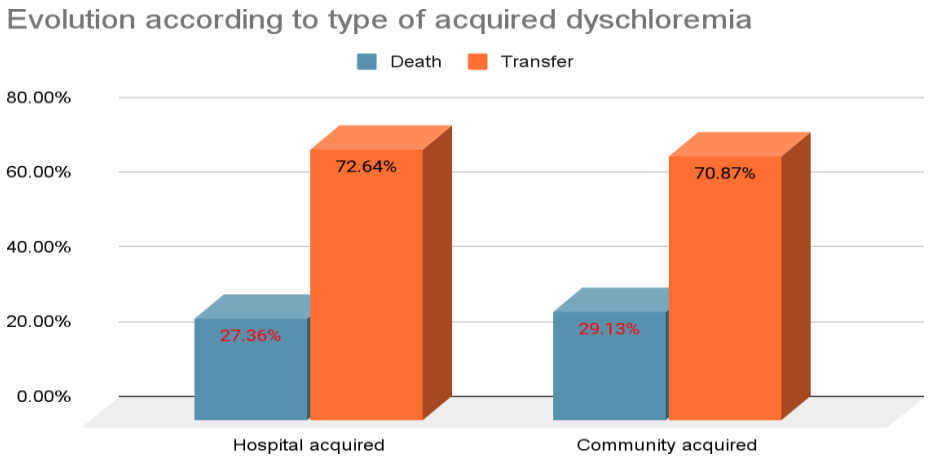

Figure 14: Mortality according to the type of acquired dyschloremia.

Discussion

1. Generalities:

A. Chloride physiology:

Chloride accounts for 70% of all anions in the body. Its normal plasma concentration is around 105 ± 2 mmol/l, while intracellular levels are generally low (around 10 mmol/l). In a healthy adult,daily chloride intake is 6 to 10 g/day in the form of NaCl and KCl.

Chloride is secreted by the digestive tract via chloride channels in the apical membrane and thesodium-potassium-chloride cotransporters in the basolateral membrane of digestive cells [1].

The amount of chloride secreted by the digestive tract varies throughout the day according tofood intake.

Kidneys play a major role in regulating chloride balance. Around 99% of chloride filtered by the glomerulus is reabsorbed: 60% in the proximal convoluted tubule, 15-20% in the loop and 5% inthe distal convoluted tubule and collector. These phenomena involve different types of tubular and intercalary cell membrane channels and co-transporters [1,2]. Only 1% of filtered chloride isultimately excreted in the urine, and it is by modulating urinary chloride excretion that the kidneyregulates plasma Ph.

Chloride is a strong anion, and is therefore present in dissociated form in plasma. As such, it plays a fundamental role in the acid-base balance. As it cannot be metabolized, its accumulation leads to the development of metabolic acidosis with a high anion gap (according to Henderson-Hasselbalch). Furthermore, following Stewart's concept, metabolic acidosis results from the decrease in plasma strong ion difference (SID) caused by elevated chloride [3]. The impact of the transcellular movement of chloride via its various membrane transporters hasbeen widely illustrated experimentally [4,12]. It is via these transporters that chloride plays a major role in cell volume regulation. These regulatory functions are mainly triggered by changes in intracellular chloride concentration or cell volume.

Chloride channels are membrane proteins, some of which are activated by voltage-gated chloride channels (VGCs) triggered by cAMP, Calcium, GABA or Glycine [4,13], while othervoltage-independent family (CICs) are thought to be particularly involved in cell volume regulation, cell multiplication and apoptosis [7].

Transmembrane movement of chloride can also take place via anion and/or cation cotransporter systems such as NA+ /CL- (NCC), K+ /CL- (KCC) or NA+ /K+ /2 CL- (NKCC) [8,9,14], and morerecently CL- /HCO3- anion exchangers, which include the SLC4, AE3 and SLC26A11 families [13,15]. NCCs and KCCs facilitate the entry of sodium, chloride and potassium into the cell; these transfers are inhibited by elevated intracellular chloride concentrations. KCCs promote the extrusion of chloride and potassium from the cell, an exchange stimulated by falling intracellularchloride concentration [16].

Plasma hypertonicity activates the NKCC1 cotransporter, which increases the intracellular concentration of NA+, K+ and CL-, thereby restoring cell volume: this is known as RegulatoryVolume Increase or RVI.

In this way, intracellular dehydration caused by plasma hypertonicity is reduced. Plasma hypotonia, on the other hand, activates KCC3, and thus the cellular extrusion of K+ and CL- withwater. As a result, the transmembrane osmotic gradient becomes almost zero, which limits cellular oedema: this is known as Regulatory Volume Decrease or RVD [8,9,17].

A study by Djikistra et al. showed that chloride penetration into cells (combined with Na+ ororganic anions) induced cellular edema, whereas exclusive sodium enrichment (without chloride) had no effect [18].

2. Epidemiology of dyschloremia in intensive care units:

In recent years, various studies have led to growing interest in the correlation between chloride and its effects on critically ill patients. Both hypochloremia and hyperchloremia are associated with more serious clinical outcomes, including death and acute renal failure [19].

A. Age and gender:

In our study, the age group over 55 years represented the majority of patients, this is consistentwith several studies conducted in the intensive care setting which have objectified a predominance of dyschloremia in older subjects [20], [21], [22].

Study	Patient age
Neyra et al [20]	66 years old
Huang et al [21]	56 years old
McCluskey et al [22]	63 years old
Thongprayoon et al [23]	63 years old
Our study	55 years old

Table 5: Comparison of literature data according to patient age.

With regard to the gender of our patients, we noted a clear predominance of male patients, a finding echoed by Huang et al. and Thongprayoon et al. [21, 23]. However, the study by McCluskey et al. showed that dyschloremia was predominantly present in female patients [22].

B. Onset of dyschloremia:

The study by Shao et al found that the incidence of dyschloremia on admission to intensive careunits was high, reported at 37% [24], whereas in our study we found a higher rate of dyschloremia on admission, which was present in 49.3% of subjects. Since dyschloremia can result from the pathological process or therapeutic interventions [25], our findings may be related to the severity of the patients' pathology, given that their most frequent reasons for hospitalization were polytrauma, head trauma and stroke, as reflected by the Glasgow score in our patients, which was below 10 in 70% of cases.

Furthermore, Thongprayoon et al [23] found that 41% of patients had acquired dyschloremiaduring hospitalization. Our results showed that 27.30% of our patients acquired dyschloremiaduring the first 48 hours after admission to the ICU, and 61% received vascular filling with saline. This may be explained by the strong association between hyperchloremia and the administration of chloride-rich fluids such as 0.9% saline [25,26].

3. Effects of chloride on organ function:

A. Effects of chloride on kidney function:

Chloride is the most abundant anion in the extracellular compartment, and is regulated by thekidneys. The amount of chloride excreted in the urine depends on the amount filtered by the glomeruli and on exchanges along the nephrons.

Under normal circumstances, over 60% of the filtered chloride is reabsorbed by the proximaltubules.

While hyperchloremia can be the consequence of renal failure, several studies suggest that itcan also induce acute kidney injury (AKI).

Several experimental studies have confirmed that high concentrations of chloride in the renal artery induce vasoconstriction responsible for a drop in renal blood flow and glomerular filtration rate, proportional to the rise in chloraemia [27,28]. The intra-renal hemodynamic effects of chloride mainly involve the tubuloglomerular feedback mechanism via the macula densa.

Schematically, hyperchloremia in the glomerular afferent arteriole induces a reduction in proximal tubular reabsorption, the resulting increased chloride entry into macula densa cells releases adenosine, which stimulates its alpha 1 receptors and induces vasoconstriction of the afferent arteriole, ultimately lowering renal blood flow and glomerular filtration rate [2,29]. Thisvasoconstriction may be linked to thromboxane release and an increased response to renal vasoconstrictors such as angiotensin II [30,31].

Water and sodium overload (linked to saline crystalloid intake) may also alter renal tissue perfusion by creating edema and renal congestion [32].

To assess the impact of chloride on renal function, retrospective observational cohort studies have been carried out in the ICU, most of them involving heterogeneous patient populations [20,33-36]. The main results of these studies show discordant results depending on the chosen criteria, and provide no evidence in favor of a causal relationship between hyperchloremia, AKI or recourse to extra renal cleansing (ERT).

B. Effects of chloride on brain function

Intracellular chloride concentration regulates neuronal excitability by modifying gabaergic neurotransmission via GABA-activated chloride channels [15,36]. All cerebral aggressions trigger activation of cerebral excitotoxicity, resulting in glutamate release and cerebral edema [9,12]. Glutamate-induced activation of N-Methyl-D-Aspartate (NMDA) receptors promotes cellular chloride uptake by opening "GABA-gated" chloride and volume-sensitive chloride channels. In the event of sustained activation, cerebral edema develops, followed by cellular necrosis. Conversely, the reuptake and disappearance of glutamate facilitates cellular extrusionof chloride (and potassium) by activating the same channels [11]. These same cell volume regulation mechanisms are activated by osmotic variations or ischemia [8].

Cerebral ischemia induces metabolic changes in intracellular concentration, characterized byintracellular accumulation of sodium, calcium versus extracellular chloride and potassium.

These changes are present in many brain cells (neurons, astrocytes and endothelial cells of theblood-brain barrier), leading to the development of cerebral edema and brain death [5,6,10].

Pond et al [6] showed that inhibition of NKCC1 and KCC2 cotransporters by furosemide or bumetanide restored cellular ATP storage and reduced neuronal damage in ischemia-reperfusion without glucose supply. In a similar model, NKCC1-deleted mice showed a30-45% reduction in the area of cerebral infarction compared to wild-type mice [10]. Inhibition of NKCC1 reduces astrocytic neuronal cell edema and cerebral excitotoxicity [5,11,12].

Recent work confirms the major role of the CL- /HCO3- cotransporter in the development of neuronal cell edema via the SLC26A11 cotransporter [13] and in the maintenance of acid-basebalance in the renal tubule via the AE1 and CIC cotransporters [17].

C. Effects of chloride on heart function:

In the myocardium, the equilibrium potential of chloride is more positive than the restingmembrane potential.

Extracellular chloride removal produces only small changes in the resting membrane potential of cardiac muscle, indicating that the resting membrane potential is higher. Yet, chloride removal is capable of producing dramatic changes in the action potential pattern suggesting that chloride conductance may increase during depolarization [37,38].

In previous years, studies by Hutter and Noble [38] and Carmeliet [37] were the first to investigate the possibility that chloride anions play an important role in the regulation of cardiacelectrical activity. Numerous investigations have in fact led to an understanding of the possible contribution of chloride conductance to the resting membrane potential and to the generation ofcardiac action [39]. And others have shown that an increase in chloride conductance is largely responsible for the initial rapid repolarization phase of the action potential of cardiac Purkinje fibers [40, 41].

The study by Testani et al. showed that WNK kinases as chloride-sensitive kinases provide a possible mechanism by which hypochloremia could participate directly in the pathophysiology of heart failure. Since their initial description, WNK kinases, and in particular WNK1 and WNK4, have become key regulators of blood pressure and electrolyte balance [42,45]. In addition, mutations in WNK1 and WNK4 have been shown to cause hypertension, hyperchloremic metabolic acidosis and hyperkalemia through increased renal reabsorption of sodium chloride [43, 46 ,47].

D. Effects of chloride on the gastrointestinal system:

Chloride is absorbed by almost the entire intestine during food digestion. Chloride intake rangesfrom 7.8 to 11.8 g/day for adult men and 5.8 to 7.8 g/day for adult women in the USA [48]. Most of the chloride in the body comes from table salt (NaCl) in the diet, but also from salt-containing foods [49]. Chloride ions are secreted into the gastric juice in the form of hydrochloric acid (HCl).

Regulation of gastric acid secretion requires the coordinated function of various parietal cell's apical and basolateral ion transport pathways, as well as the fusion of tubulovesicles containingH+/K+-ATPases with the apical membrane at rest and their endocytosis after removal of the secretory stimulus [50]. The parietal cell secretes acid against an enormous gradient (over 106-fold) by the ATP-driven exchange of one H+ for one K+ at the apical plasma membrane viathe H+/K+ ATPase enzyme. HCl secretion aids protein digestion by activating pepsinogen to pepsin, which kills most food-borne organisms, prevents bacterial or fungal proliferation in the small intestine, promotes the flow of bile and pancreatic enzymes, and facilitates the absorption of various nutrients, including folic acid, ascorbic acid, beta-carotene, non-heme iron and some forms of calcium, magnesium and zinc. In addition, Intrinsic factor is activated to ensure absorption of vitamin B12. Hydrochloric acid aids the release of iron from food and facilitates itsconversion to ferrous form [51].

Basal HCl production is less than 11 mmol/hour and increases from 10 to 63 mmol/hour withmeals [52]. Around 8 liters of fluid are secreted daily into the human intestinal tract.

As water cannot be actively secreted, the driving force behind fluid flow is the osmotic gradient between the intestinal lumen and the mucosa. The osmotic gradient responsible for drawing water into the intestine is mainly generated by the secretion of Cl- and, to a lesser extent, HCO3-, with Na+ following passively through the paracellular space [53-55]. Currently, three channels have been identified by which Cl- can be secreted into the intestinal lumen, creating the osmotic gradient driving fluid secretion, namely: cystic fibrosis conductance regulator (CFTR); calcium-activated chloride channels (CaCC); and type 2 chloride channels (ClC-2). Theprecise role of these channels remains to be elucidated [55,56].

All in all, in the gastrointestinal tract, chloride has two unique functions: on the one hand, it is secreted as part of the hydrochloric acid in the stomach that contributes to protein digestion, controlling microorganisms and the absorption of certain important nutrients/minerals [17]; on the other hand, it main it maintains the gastrointestinal osmotic gradient and fluid secretion.

4. Dyschloremia in the ICU

Despite the constant chloride concentration changes during hospitalization, chloride abnormalities receive less attention than any other electrolytes routinely measured. In recent years however, chloride abnormalities in intensive care units have started to receive considerable attention, particularly hyperchloremia as one of the main causes of metabolic acidosis [57] and hypochloremia as one of the main causes of metabolic alkalosis [58,59].

A. Hypochloremia:

Hypochloremia is defined as a blood chloride level below 95 millimoles/liter. Hypochloremia in intensive care and post-anesthesia care units may be due to disease-related pathophysiological processes or secondary to therapeutic interventions [17,60].

The main causes of hypochloremia are related to gastrointestinal or renal losses of chloride ions (Table VI). Renal losses of chloride ions may occur in the clinical setting of diuretic use [60] or, more rarely, in the setting of renal disorders such as Bartter's syndrome. Gastrointestinal lossesmay occur through loss of chloride-rich fluids (e.g. vomiting). Hypochloremia can also develop with excessive water gains (e.g., syndrome of inappropriate antidiuretic hormone secretion and congestive heart failure) [17,25].

The reported prevalence of hypochloremia varies according to clinical setting and patient population. In the general intensive care setting, various studies have reported an incidence of between 6.7% and 37% [24,61,62,63]. In contrast, we noted that in our series hypochloremia was mentioned in 85.2% of our patients. This may be linked to the frequency of chronic vomiting (19.5%) or the use of diuretics in our patients (11.5%), the latter being one of the most renowned causes of hypochloremia in literature.

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

Table 6: Mechanisms and etiologies of hypochloremia.

B. Hyperchloremia:

Hyperchloremia is defined as a blood chloride level in excess of 105 millimoles/liter. Hyperchloremia, in contrast to hypochloremia, has recently received a great deal of medical attention. Rates of occurrence of hyperchloremia in the ICU vary considerably depending on thepopulation studied and the time of measurement [19].

The mechanisms leading to the development of hyperchloremia include, firstly, the iatrogenicmechanism of excessive chloride administration during the management of patients with chloride solutions; secondly, excessive water loss, either net water loss or chloride loss. In addition, increased renal reabsorption of chloride is another causal mechanism ofhyperchloremia (Table 7) [19].

In our study, we found that hyperchloremia was present in 14.8% of patients. Our results also revealed a number of clinical features that could explain the frequency of hyperchloremia in our department, notably: diabetes (22.5%), use of diuretics (11.5%), fever (1.91%) and excessive vascular filling with saline (61%).

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

Table 7: Causes of hyperchloremia [19].

C. The role of vascular filling in dyschloremia:

Vascular filling is the first step in increasing blood volume (= effective blood volume) and restoring adequate hemodynamics in patients. It is the most commonly used therapeutic intervention in life-threatening emergencies, whether in the pre-hospital, emergency or intensive care setting [64,65]. There are several types of vascular filling solution: natural colloids such asalbumin, synthetic colloids (HEA, gelatins, dextrans) and crystalloids [66].

Crystalloids are composed of water and electrolytes. Today, they are the first-line solution of choice for vascular filling. They are characterized by different compositions, in particular for chloride and the presence of metabolizable anions (Table 8). The common rule is the need for equality between positive and negative charges. Unbalanced solutes are characterized by highchloride concentrations: these are saline solutes such as 0.9% NaCl, mistakenly referred to as saline. Whatever their osmolarity (0.9%, 3%, 7.5%), all these solutions have a chloride concentration equal to that of sodium, which inevitably leads to hyperchloremic acidosis by reducing the difference in strong plasma ions (SID) [67,68,69]. Balanced crystalloids are characterized by a chloride concentration closer to that of plasma (the oldest being Ringer Lactate). To balance the positive and negative charges, it is therefore necessary to add other metabolizable anions to the solution. These solutes have an osmolarity closer to that of plasmathan non-balanced solutes.

The choice of the optimal crystalloid fluid in intensive care units has been debated recently. Therelationship between imbalances in chloride concentrations and the severity of illness was the trigger for this debate. In particular, hyperchloremic acidosis induced by unbalanced solutes Randomized controlled trials have addressed the conundrum of the use of chloride-rich solutions (0.9% saline) versus balanced, more chloride-limited crystalloid solutions (e.g. Ringer's lactate, Plasmalyte) [69, 70,71].

As early as 1911, Evans [72] warned against the excessive chloride intake associated with 0.9% saline. And it was following questionable in vitro experimental work that 0.6% saline was abandoned in favor of 0.9% saline [73]. This finding has been demonstrated by several studies evaluating the relationship between hyperchloremia and the administration of chloride-rich solutions [25,26]. Some other studies have managed to find contradictory results [21,74].

In a recent randomized cluster and crossover study, Semler et al [33] compared the morbidity and mortality of 974 intensive care and post-anesthesia care patients receiving 0.9% NaCl versus balanced fluids. The results showed no significant difference on a composite score associating mortality, extrarenal replacement therapy (ERT) or persistent renal dysfunction at 30days. However, in patients receiving total fluid volumes > 6 L, the difference became significantin favor of the balanced group.

Solutés	Na^+ (meq/L)	K+ (meq/L)	Cl^- (meq/L)	Autres anions (meq/L)	Osmolarité (mosm/L)	SID in vivo (meq/L)
Cristalloïdes						
Non balancés						
NaCl 0,9 %	154	0	154	–	308	–
NaCl 3 %	510	0	510	–	1026	–
NaCl 7,5 %	1275	0	1275	–	2395	–
Balancés				Lactate (27,6)		
Lactate Ringer	130	4	108	Acétate (29)	277	27
Acétate Ringer	132	4	110	Acétate (27)	277	27
Acétate Gluconate	140	5	98	Gluconate (23)	294	50
(Plasmalyte®)				Acétate (24)		
Acétate Malate (Isofundine®)	145	4	127	Gluconate (23) Acétate (24) Malate (5)	304	27
Colloïdes						
Non balancés						
Hydroxyéthylstarch	154	0	154	–	308	–
(Voluven®)						
Albumine	154	0	154	–	308	–
Balancés						
Hydroxyéthylstarch (Tetraspan®)	140	4	118	Acétate (24)	297	29
Hydroxyéthylstarch (Hextend®)	143	3	124	Malate (5)	307	28
Gélatines 4 % (Plasmion®)	154	0	120	–	307	32
Gélatines 3 % (Gélofusine®)	150	0	100	–	284	56

Table 8: Classification of different IV fluids according to their ionic composition and osmolarity[98].

5. **Morbidity and mortality:**

A. **Morbidity/ Complications:**

A.1. Metabolic acidosis: Hyperchloremic acidosis is increasingly recognized as a clinical entity, a new "enemy within",which has gone unnoticed for decades. Although the associated morbidity may be subtle at present, current data tend to suggest that hyperchloremic acidosis may have adverse consequences that can be circumvented by the use of balanced solutions. These consequences, both theoretical and clinical, may result from hyperchloremia, acidosis or both [75].

A.2. Cerebral complications: In a study comparing filling with lactated Ringer's or isotonic saline, healthy volunteers in the latter group showed minor difficulties in concentrating, particularly when reading or performing simple arithmetic tests [76]. This was not observed in volunteers who received Ringer's lactate solution. In another study, the same finding was made in patients treated with saline versus those given lactated Ringer's [77].

A.3. Renal complications: In dogs, chloride loading induced renal vasoconstriction [78]. In the above-mentioned study in healthy volunteers, there was a delay in first diuresis in the saline group compared with the lactated Ringer's group (106 min vs. 76 min) [76].

In another clinical study, diuresis was lower (717 mL) in patients infused with saline than with lactated Ringer's (1,075 mL) [57]. Finally, two studies comparing patients receiving isotonic saline with patients receiving balanced electrolyte solution found in both cases a decrease in diuresis with isotonic saline versus balanced electrolyte solution [77, 79].

In our study, acute renal failure was reported in 14.83% of our patients with dyschloremia. This link between dyschloremia and acute renal failure (ARF) has been elucidated by several studies, including Shao and Zhang and colleagues [24,34] who found an association between peak chloride level and the incidence of ARF. However, chloride levels at ICU admission were not associated with the development of AKI. They also found that mean chloride levels were higher in patients with AKI. Another study found an increased rate of AKI in patients with septicshock with a moderate increase in chloremia (a change of at least 5 mmol / l) even without hyperchloremia [82]. However, a study of patients with ST-segment elevation myocardial infarction who underwent percutaneous interventions failed to demonstrate a direct association between hyperchloremia and AKI [70].

A.4. Digestive complications: As in the case of the kidney, saline loading may cause vasoconstriction of the splanchnic circulation. Indeed, in two studies, patients infused with isotonic saline had more nausea and vomiting than those infused with either a balanced electrolyte solution or lactated Ringer's [76,77].

A.5. Biological complications:

Blood count: Experimentally, it has been shown that saline can cause lysis of red blood cells and consequently induce anemia [80]. This phenomenon was observed to a lesser degree when colloids such as gelatin, starch and especially

albumin, with a lower chloride load, were used. Ina cohort study by Neyra et al. anemia was found in most dyschloremic patients [20], while in ourstudy hemoglobin levels were also reduced in half our patients.

- **Hemostasis work-up:** Perioperative bleeding was significantly less in the groups receiving balanced electrolyte solution or lactated Ringer's compared with those receiving isotonic saline [57, 79]. In one of thetwo studies, this difference was attributed to a significant slowdown in the onset of clot formationmeasured by thromboelastogram in the isotonic saline group [79]. However, in a study by Handy et al. on aortic aneurysm surgery, it was shown that, although there were no major differences between the use of saline and Ringer's lactate, blood product requirements were greater in the saline group [75].

B. **Mortality:**

Acid-base disorders are common in intensive care patients and are generally associated withincreased morbidity and mortality [83]. Several studies on the role of chloride in critically ill patients have evaluated the association between dyschloremia and mortality in this population[84].

For example, hyperchloremia [20, 85-87] and hypochloremia are associated with increased in-hospital mortality in critically ill patients [88-90]. However, other retrospective observational cohort studies evaluating the impact of chloraemia on renal function and mortality (Table X)

have shown conflicting results depending on the endpoints chosen, and no evidence in favor of a causal relationship between hyperchloraemia, AKI, use of RRT or mortality [20, 34,82,85,86,91, 92].

Study	Population, n	Results
Zhang et al.	**No selection, 1221**	Hyperchloremia is associated toan increase in AKI occurrence with no effect on mortality
Neyra et al.	**Sepsis and septic shock, 1940**	Hyperchloremia is associated toan increase in intrahospital mortality rates, independently ofAKI occurrence
Raghunathan et al.	**Septic shock, 6370**	The use of "balanced" IV fluids decreases the mortality at D-90 dependently of infused volumes
Suetrong et al.	**Sepsis and septic shock, 240**	Chloremia variations up to 5 mmol/L (even in absence of hyperchloremia) lead to an increase in AKI incidence, with no influence on mortality
Regenmortel et al.	**No selection, 6480**	Hyperchloremia is associated toan increase in mortality at D-30and in hospital settings
Tani et al	**No selection, 448**	No relationship between chloremia and patient outcome
Shaw et al	**SIRS, 3116**	The use of NaCl 0.9% leads tomore use of dialysis
Shaw et al	**SIRS, 109836**	The use of a chloride-controlled infusion strategy was associated to a decrease in hospital mortality independentlyof infusion volumes
Sen et al	**No selection, 4710**	There is no correlation betweenchloride load and AKI. But, every increased by 100 mEq inchloride load was associated to a 1 year mortality increase of 5.5%

Table 10: Retrospective observational cohort studies evaluating the impact of chloride on renalfunction and/or mortality [99].

In the literature, numerous studies of patients with dyschloremia in different hospital units have recorded an incidence of mortality that has varied between 4.8% and 15.1% [21,23,93]. In ourstudy we noted a higher overall mortality rate (28.23%). This may be explained by the nature and the severity of the surgical pathologies for which our patients were admitted (polytrauma, head trauma, ...).

In addition, we found varying mortality rates depending on the type of dyschloremia. Mortalitydue to hyperchloremia was higher than in patients with hypochloremia (87.10% vs. 17.98% respectively). This difference was also found in the study by Thongprayoon et al. The authors found a higher mortality rate in patients with hyperchloremia (3.5%) than in patients with hypochloremia (0.9%) [23].

In a retrospective study of 76 719 hospitalized patients, alterations in chloraemia on admission or during hospitalization increased the risk of worsening disease prognosis and mortality [94]. On the one hand, hyperchloremia on admission has been associated with an increased risk of adverse patient outcomes, including a higher incidence of acute kidney injury and longer hospital stay [20,22,23,34,94,95,96,97]. In the same way, hypochloremia during hospitalization represents a significant risk factor for in-hospital mortality and acute kidney injury, irrespective of serum chloride levels on admission [23,95].

Our study results join those of the other previously cited series, as we have found a slightlyhigher mortality rate in patients with acquired dyschloremia (29.13%) than in those with dyschloremia on admission (27.36%).

Our work shows that:

- Dyschloremia induced by unbalanced saline solutions is responsible for excess mortality and morbidity in intensive care and perioperative patients.
- It is therefore legitimate to promote the preferential use of balanced solutions when infusing large volumes of solutions during vascular filling, as they reduce the incidence ofacute renal failure. Unbalanced solutions are still recommended in cases of hypochloremic metabolic alkalosis, or for low-volume infusions.

Conclusion

Chlorine is the most abundant strong anion in the body. It plays a major role in cell volume regulation, as well as in numerous other organ functions, including immune function, arterial vasomotricity, coagulation and neuromuscular excitability.Fluctuations in its concentrations canhave deleterious effects on the patient.

Dyschloremia is a common complication observed in intensive care unit patients. They can beclassified into two categories: hypochloremia and hyperchloremia. The latter is mostly due to a pathological process, or to therapeutic interventions such as vascular filling with chlorine-rich solutions.

The results of our study show that the incidence of dyschloremia is high in the surgical resuscitation setting. We also found that the prevalence of hypochloremia was higher thanhyperchloremia.

Concerning the association between dyschloremia and mortality, the mortality rate was veryhigh in subjects with hyperchloremia and in patients who acquired dyschloremia during hospitalization.

Fluctuations in blood chlorine concentrations were a risk factor for excess mortality and morbidity in critically ill patients. To date, many studies have focused on the role of unbalanced saline solutions in inducing acquired hyperchloremia, which is responsible for numerous organ complications, and on the benefits of using balanced solutions when infusing large volumes.

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