European Journal of Internal Medicine 23 (2012) 203–211

Contents lists available at SciVerse ScienceDirect

European Journal of Internal Medicine

journal homepage: www.elsevier.com/locate/ejim

Review article

Chloride: The queen of electrolytes?

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ARTICLE INFO

Article history:
Received 19 August 2011
Received in revised form 20 October 2011
Accepted 22 November 2011
Available online 21 December 2011

Keywords:
Chloride
Acid–base
Hyperchloremic
Hypochloremic

ABSTRACT

Background: Channelopathies, defined as diseases that are caused by mutations in genes encoding ion channels, are associated with a wide variety of symptoms and have been documented extensively over the past decade. In contrast, despite the important role of chloride in serum, textbooks in general do not allocate chapters exclusively on hypochloremia or hyperchloremia and information on chloride other than channelopathies is scattered in the literature.
Study design: To systematically review the function of chloride in man, data for this review include searches of MEDLINE, PubMed, and references from relevant articles including the search terms "chloride," "HCl," "chloride channel" "acid-base," "acidosis," "alkalosis," "anion gap" "strong anion gap" "Stewart," "base excess" and "lactate." In addition, internal medicine, critical care, nephrology and gastroenterology textbooks were evaluated on topics pertaining the assessment and management of acid-base disorders, including reference lists from journals or textbooks.
Conclusion: Chloride is, after sodium, the most abundant electrolyte in serum, with a key role in the regulation of body fluids, electrolyte balance, the preservation of electrical neutrality, acid-base status and it is an essential component for the assessment of many pathological conditions. When assessing serum electrolytes, abnormal chloride levels alone usually signify a more serious underlying metabolic disorder, such as metabolic acidosis or alkalosis. Chloride is an important component of diagnostic tests in a wide array of clinical situations. In these cases, chloride can be tested in sweat, serum, urine and feces. Abnormalities in chloride channel expression and function in many organs can cause a range of disorders.

1. Introduction

The study of chloride channels of membranes has seen an explosion of interest over the past decade and exciting recent developments have sparked renewed interest in this field. In contrast, despite the prominent concentration of chloride in serum, textbooks in general do not allocate chapters exclusively on chloride or hypochloremia and hyperchloremia. About thirty years ago, chloride (Cl^-) was called "the queen of electrolytes" in a teaching class on acid–base pathophysiology. Using a chess analogy, sodium can be seen as the "king", -being the most prominent electrolyte-, and chloride perhaps as the "queen". Although chloride was the first electrolyte to be easily measured its importance always has been overshadowed by other major serum electrolytes [1,2], seemingly serving as a sort of appendix of sodium or potassium or just a stand-in for bicarbonate. The purpose of this review is to determine if a much more prominent role, or metaphorically speaking "royal status" for chloride in humans is justified.

2. Characteristics and functions of chloride

Chloride has a molecular weight of 35.5 and it is the body's principle anion [2,3], of which it represents 70 percent of the total negative ion content. On average, an adult human body contains approximately 115 grams of chloride, making up about 0.15 percent of total body weight. Chloride is the most important extracellular anion, serving many body functions including the maintenance of osmotic pressure, acid–base balance, muscular activity, and the movement of water between fluid compartments [1,4].

Chloride channels are pore-forming membrane proteins that allow the transport of Cl^- across biological membranes. Chloride channels are ubiquitously expressed in almost all eukaryotic cells and are essential in maintaining health. In the past decade, there has been remarkable progress in understanding of the roles of Cl^- channels in the development of human diseases. Genetic studies in humans have identified mutations in the genes encoding Cl^- channels that lead to a loss of Cl^- channel activity [5,6]. Chloride channel dysfunction is involved in the development of a broad spectrum of diseases, including dystrophia myotonica (inhibition of the chloride conductance due to loss of ClC-1 channel activity), cystic fibrosis (defective chloride transport into the epithelial cells), chronic

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0953-6205/$ – see front matter
doi:10.1016/j.ejim.2011.11.013

pancreatitis (inhibition of chloride channel activity caused by cystic fibrosis transmembrane conductance regulator mutations [CFTR]), bronchiectasis (possible due to defective CFTR activity in lung), congenital bilateral aplasia of the vas deferens (chloride channel dysfunction), hereditary hyperekplexia (reduction in chloride conductance), epilepsy (stimulation of chloride influx through chloride channels may result in tonic inhibition of the electrical activity in neurons), cataract (reduced activity of volume-activated chloride channels in the plasma membrane of the lens) the growth of glioma cells (defect in the volume-activated chloride channels in glioma cells), and Bartter's disease (decreased renal tubular chloride transport that leads to a reduction of NaCl reabsorption) [5–7].

3. The gastrointestinal tract and chloride

Chloride is absorbed by almost the entire intestine during food digestion. The chloride intake ranges from 7.8 to 11.8 g/day for adult men and 5.8 to 7.8 g/day for adult women in the United States [8]. Most of the chloride in the body comes from table salt (NaCl) in the diet, but also from salt-containing foods [1].

Chloride ions are secreted in the gastric juice as hydrochloric acid (HCl). The regulation of gastric acid secretion requires the coordinated function of a variety of parietal cell apical and basolateral ion transport pathways, as well as the fusion of H^+/K^+-ATPase-containing tubulovesicles with the resting state apical membrane and their endocytosis after withdrawal of the secretory stimulus [9]. The parietal cell secretes acid against a huge gradient (greater than 10^6-fold) by ATPdriven exchange of one H^+ for one K^+ at the apical plasma membrane via the enzyme H^+/K^+-ATPase.

HCl secretion assists protein digestion by activating pepsinogen to pepsin, which kills most foodborne organisms, prevents bacterial or fungal overgrowth of the small intestine, encourages the flow of bile and pancreatic enzymes, and facilitates the absorption of a variety of nutrients, including folic acid, ascorbic acid, beta-carotene, nonheme iron, and some forms of calcium, magnesium, and zinc. Intrinsic factor is activated in order to absorb vitamin B_{12}. Hydrochloric acid aids in the liberation of iron from food and facilitates its conversion to the ferrous form [10]. Basal output of HCl is below 11 mmol/hour, increasing to 10 to 63 mmol/hour with meals [2]. The acid solution contains 160 mmol of HCl per liter resulting in a pH of 0.8. At this pH, the $[H^+]$ is about 3 million times that of the arterial blood and this high concentration of protons is responsible for the effects of gastric acid [11]. Approximately 8 l of fluid is secreted into the human intestinal tract on a daily basis. Since water cannot be actively secreted, the driving force for fluid flux is the osmotic gradient between the lumen of the intestine and the mucosa. The osmotic gradient responsible for pulling water into the intestine is mainly generated by Cl^- and, to a smaller extent, HCO_3^- secretion, with Na^+ passively following through the paracellular space [12–14]. Currently, three channels have been identified through which Cl^- can be secreted into the intestinal lumen, thus creating the driving osmotic gradient for fluid secretion, namely: the cystic fibrosis conductance regulator (CFTR); calcium-activated Cl^- channels (CaCC); and chloride type-2 (ClC −2) channels. The definite role of these channels remains to be elucidated [14,15].

Three mechanisms determinate chloride transport in the basolateral membrane: the Na^+–K^+–$2Cl^-$ cotransporter, potassium channels and the Na^+-K^+-ATPase. The ability of the intestine to secrete fluid depends on the Na^+–K^+–$2Cl^-$ cotransporter (NKCC), which mediates Cl^- uptake at the basolateral pole of enterocytes and thereby provides the substrate for apical Cl^- secretion [12,14]. Potassium channels located in the basolateral membrane are believed to maintain cellular electroneutrality by compensating for Cl^- efflux and keeping the cell in a state of hyperpolarization, which in turn enables sustained Cl^- transport across the apical membrane [16]. The Na^+–K^+-ATPase provides the energetic requirements for active Cl^- secretion by transporting three Na^+ ions out of the cell and two K^+ ions into the cell at the cost of one molecule of ATP [14,17,18]. Enterocyte chloride secretion is controlled by a variety of endocrine, paracrine, autocrine, neuronal and immunological effectors. The classical and well-characterized second messengers that modulate intestinal ion transport are cAMP, cGMP and free cytosolic Ca^{2+} [12,14].

4. The extracellular space

The exact measurement of $[Cl^-]$ in serum samples is important for correct diagnosis and therapy, and knowledge of the interference factors which influence the analytic method used, ensures correct reading of laboratory data. Measured plasma chloride concentration may differ substantially between assays. With paired samples, the mean difference (bias) in plasma chloride concentration between central laboratory and point-of-care assays can be 1.0 mmol/l (95% limits of agreement, –6.4 to 4.6 mmol/l) [19]. Many patients classified as having a normal sodium, chloride, or anion gap value with one technology may have an abnormal value with the other. In one study close to 50% of these patients had a high anion gap with one technique but a normal anion gap with the other. Preanalytical errors may include a high proportional volume of heparin in the blood gas syringe, but point-of-care blood gas analyzers, often test a lower sodium concentration and a higher chloride concentration, due to differences in electrode characteristics [19]. Further, while the reference range for central laboratory assays is often quoted as 97 to 107 mmol/l, some machines used in central laboratories have a reference range of 100 to 110 mmol/l [2]. Chloride is responsible for about 100 of the 300 mosm/L of extracellular fluid tonicity and for two-thirds of all negative charges in plasma [3,4]. Any excess chloride is passed from the body through the urine. Chloride interacts with sodium to maintain serum osmolarity and fluid balance. A shift in sodium and chloride concentration triggers a fluid volume change to restore normal solute and water ratios. To maintain acid–base balance, chloride has an inverse relationship with bicarbonate, which is part of the major chemical buffering system responsible for maintaining a normal pH when bicarbonate is lost by the kidneys or the intestines. Chloride and bicarbonate shift into and out of erythrocytes and tubuli to maintain acid–base balance. Because of its high concentration, chloride is the most important anion to maintain the balance of extracellular cations and anions to ensure electrical neutrality as the number of anions and cations in body fluids must always be equal.

5. The intracellular space

The intracellular concentration of chloride is much lower than its plasma concentration depending on the resting membrane potential of the cell. Muscle cells, for example, have a resting membrane potential of approximately −68 mV and an average chloride concentration ($[Cl^-]$) of 2 to 4 mEq/L, whereas red blood cells have a resting membrane potential of approximately −15 mV and an average $[Cl^-]$ of 70 mEq/L [20]. This higher intracellular $[Cl^-]$ in erythrocytes allows chloride to move in and out of the red blood cells very effectively, as dictated by electrical charges on either side of the cell membrane. This important difference from other cells is the basis of the so-called “chloride-shift” with the movement of chloride from the plasma into erythrocytes as blood moves from the arterial to the venous end of systemic capillaries. The Donnan ratio represents the behavior of charged particles near a semi-permeable membrane with imbalanced distribution across the two sides of the membrane. This uneven electrical charge is created by the Na^+/K^+-ATPase pump that maintains the Na^+/K^+-gradients by pumping potassium into and sodium out of the cells. The chloride shift is the result of reestablishment of equal Donnan ratios for $Cl^-$and HCO_3^-, by the presence of a special bicarbonate-chloride carrier protein in the red cell membrane. Thus, the chloride content of venous red blood cells is greater than that of

arterial red cells [11,20,21]. Since most of the CO_2 carried by the blood is in the form of HCO_3^-, the chloride shift is important because it enhances the carrying capacity of the blood for HCO_3^-. A major role of the chloride shift is therefore mitigation of the change in pH that occurs during gas transport, but also a role for O_2 unloading has been suggested [20].

6. The kidney and chloride

The chloride concentration is primarily regulated by the gastrointestinal tract and the kidneys [1]. Chloride is predominantly excreted by the kidneys. An average of 19,440 mmol is filtered through the kidneys every day, with 99.1% being reabsorbed, leaving only 180 mmol excreted per day [2].

The renal proximal tubule is responsible for most of the renal sodium, chloride, and bicarbonate reabsorption. The proximal Cl^- reabsorption proceeds mainly paracellularly, but transcellular Cl^- transport also exists by Cl^- channels and Cl^--coupled transporters. In the apical membrane, Cl^-/anion (formate, oxalate and bicarbonate) exchangers represent the first step in transcellular Cl^- reabsorption. A basolateral Cl^-/HCO_3^- exchanger contributes to the creation of an outwardly directed electrochemical Cl^- gradient across the cell membranes. This driving force favors Cl^- diffusion from the cell to the lumen and to the interstitium. In the basolateral membrane, the main mechanism for transcellular Cl^- reabsorption is a Cl^- conductance, but a Na^+-driven Cl^-/HCO_3^- exchanger may also participate in Cl^- reabsorption (Fig. 1) [22].

The amount of chloride excreted in the urine is in part related to the amount taken in by diet, infusion, or the amount required by the body. Chloride channels are expressed along the entire mammalian nephron. They participate in transepithelial chloride transport, cell volume regulation and acidification of intracellular vesicles [6].

Abnormalities in chloride channel expression and function in the kidney can cause a range of disorders [6,23]. The renal tubules are composed of highly differentiated epithelia that vary substantially in morphology and function along the nephron. The proximal tubule is responsible for reabsorbing ~60% of filtered NaCl and water. Chloride is poorly reabsorbed throughout the first segment of the proximal tubule, and a rise in chloride concentration counterbalances the removal of bicarbonate anion from tubular fluid. In later proximal tubular segments, cellular chloride reabsorption is initiated by apical exchange of cellular formate for higher luminal concentrations of

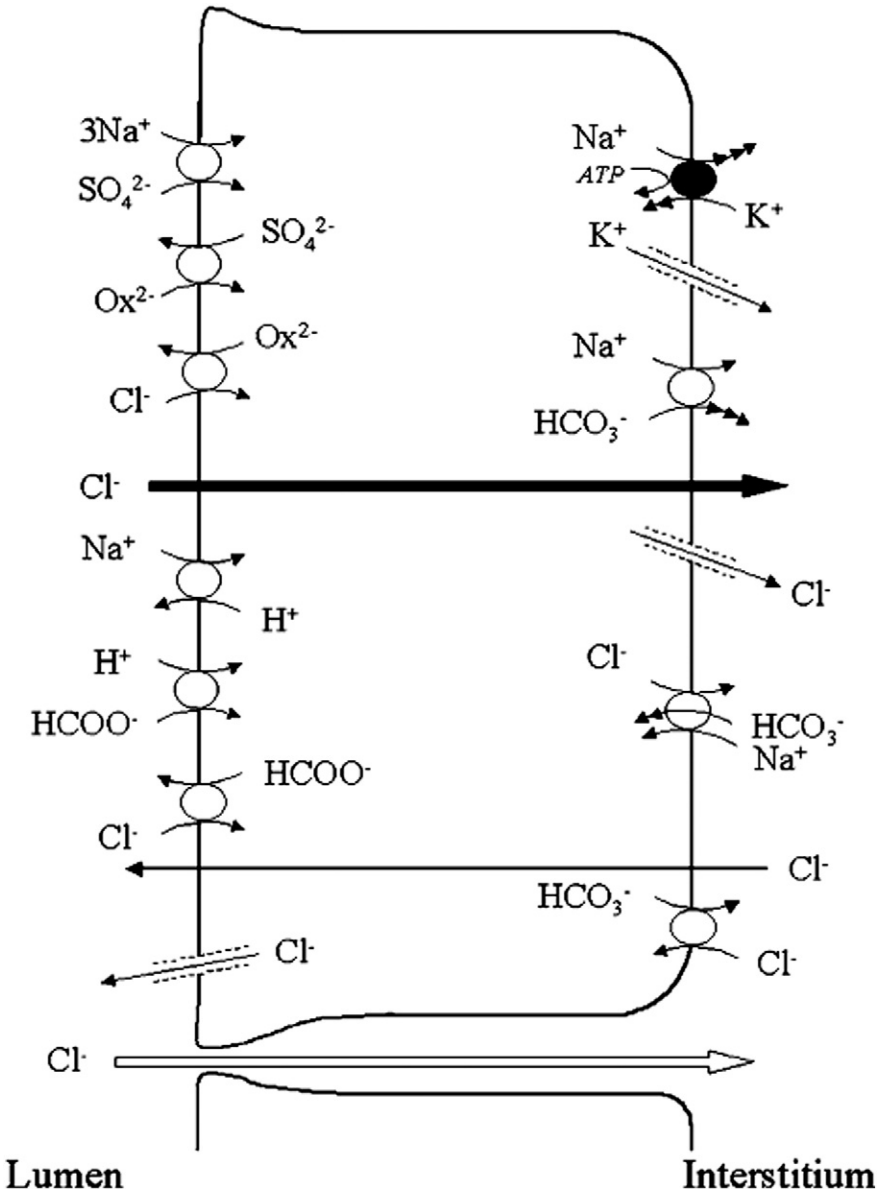

Fig. 1. Chloride transport in the proximal tubulus. From: Planelles G. Chloride transport in the renal proximal tubule. Pflugers Arch 2004;448:561–570 [22].

chloride. Basolateral chloride exit is mediated by a K^+/Cl^- co-transporter. Chloride channels play a prominent role in the proximal tubule and important examples of inherited diseases linked to defects in these channels are Dent's disease and X-linked recessive nephrolithiasis with renal failure [24].

Approximately 15–25% of filtered NaCl is reabsorbed in the loop of Henle, mainly by the thick ascending limb. In the thick ascending limb, there is a high level of secondary active salt transport enabled by the $Na^+/K^+/2Cl^-$ co-transporter on the apical membrane in series with basolateral chloride channels and Na^+/K^+-ATP-ase (Fig. 2) [25]. The macula densa and the thick ascending limb are dependent upon Cl^-. The Na^+-K^+-$2Cl^-$ cotransporter promote the entry of these ions into the cell [26–28]. At low concentrations of Na^+ or K^+, the activity of this transporter is maximally stimulated. In the physiologic range of these kations it is regulated by alterations in the concentration of Cl^- [26]. As an example, if hypovolemia is adequately treated by volume expansion it will lead to a decrease in proximal NaCl reabsorption. With the increas in the Cl^- concentration at the macula densa, the renin secretion will be reduced. In comparison, the administration of Na^+ with other anions like sodiumbicarbonate, without chloride the effect will be lower, since the tubular fluid Cl^- concentration will not rise [26,29,30].

The $Na^+/K^+/2Cl^-$ co-transporter is the primary target for loop diuretics and loss of function mutation in one of four distinct genes encoding components of the $Na^+/K^+/2Cl^-$ co-transporter (NKCC2), apical K^+ channel (KCNJ1), or basolateral chloride channel (CLCNKB, BSND) can cause variants of Bartter syndrome [24].

The distal convoluted tubule reabsorbs ~5% of the filtered NaCl. The major NaCl transporting pathway utilizes thiazide-sensitive Na^+/Cl^- co-transporter in tandem with basolateral Na^+/K^+-ATP-ase and chloride channels (Fig. 3) [31]. Loss-of-function mutations of SLC12A3 encoding the apical Na^+/Cl^- co-transporter cause Gitelman's syndrome [24]. Gordon's syndrome is caused by mutations in WNK kinases that lead to overactivity of the apical Na^+/Cl^- co-transporter in the distal convoluted tubule as the primary stimulus for increased salt reabsorption, extracellular fluid expansion, and hypertension [24]. A direct role for chloride on hypertension is not established currently, but the use of potassium rich food products that do not contain chloride, such as those found naturally in fruits and vegetables, offer larger cellular entry in exchange for sodium and greater antihypertensive effects [32]. In addition, studies show that both the renin and possibly the blood pressure responses to sodium chloride are dependent on chloride [33–35].

The basolaterally expressed $Cl^-/HCO3^-$ anion exchanger AE1 that releases bicarbonate into blood, belongs to a subfamily of electroneutral anion exchangers of the SLC4 family of bicarbonate transporters [36,37]. AE1 is abundant in the red cell membrane, where it is an integral part of the cell's cytoskeleton where it has a key role in the normal gas transfer of CO_2. It is also expressed in the basolateral membrane of the collecting duct acid secreting cell, though as a shorter N-terminally truncated form (kAE1), where it transports intracellular HCO_3^- out of the cell in exchange for Cl^-. The importance of AE1 for normal acid–base status is underlined by the fact that mutations in AE1 cause distal renal tubular acidosis [37–40]. A mouse model lacking AE1 in red blood cells and kidney demonstrated massive hyperchloremic metabolic acidosis [36]. Interestingly, mutations in AE1 in red cells can lead to hereditary spherocytosis and southeast Asian ovalocytosis, both of which have been associated with RTA [39,40].

The kidney collecting duct has an essential role in acid base transport and systemic pH homeostasis with the purpose of fine-tuning of renal acid–base secretion (Fig. 3). This important function occurs by secretion of acid into the lumen, predominantly by vacuolar H^+-ATPase and Slc26a11 (KBAT) is a potential functional partner for V H^+-ATPase in the kidney collecting duct [23]. Acid-secretory type-A intercalated cells secrete protons via a luminally expressed V-type H^+-ATPase and generate new bicarbonate released by basolateral chloride/bicarbonate exchangers including the AE1 anion exchanger, discussed below. Bicarbonate secretion is achieved by non-type-A

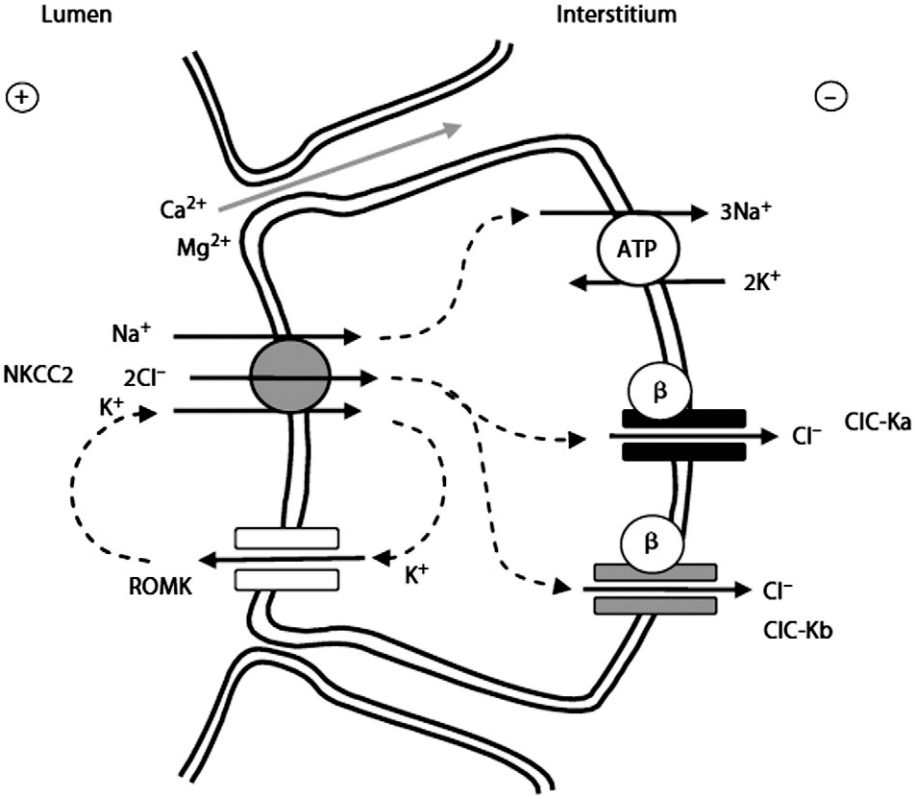

Fig. 2. Reabsorption of electrolytes in the thick ascending tubulus (TAL). From: Jeck N, Seyberth HW. Loop disorders: insights derived from defined genotypes. Nephron Physiol 2011;118:7–14 [25]. Publisher: Karger AG, Basel.

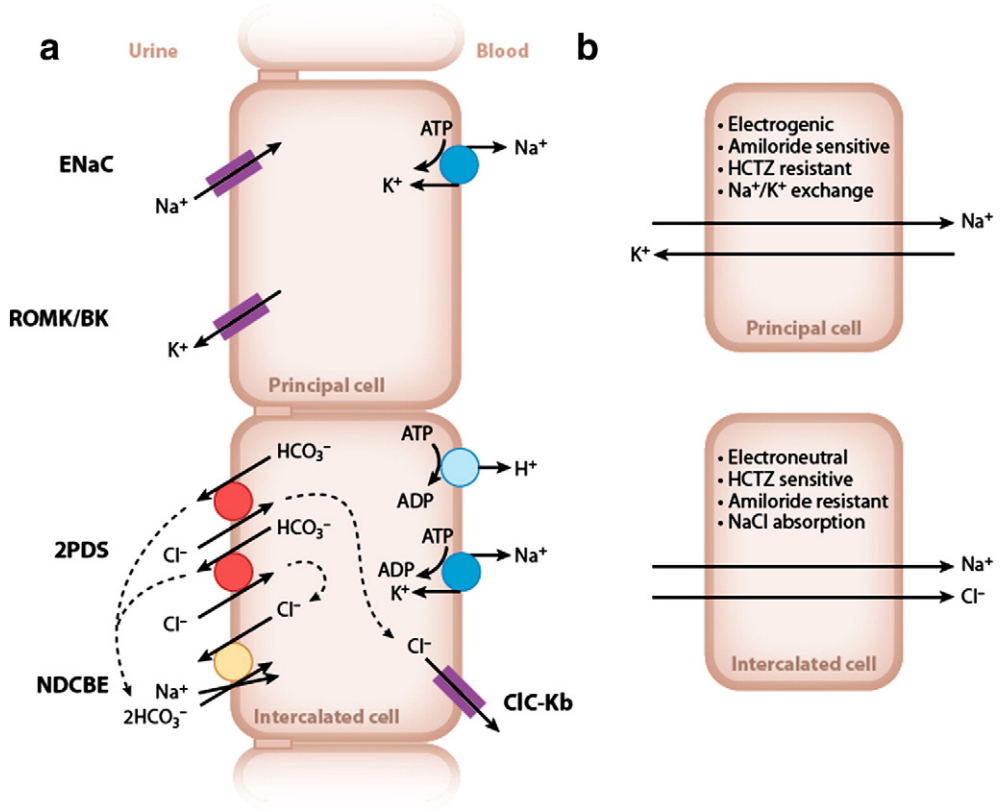

Fig. 3. Schematic model of chloride transport in the collecting duct. From: Eladari D, Chambrey R, Peti-Peterdi J. A new look at electrolyte transport in the distal tubule. Annu Rev Physiol 2012;74:4.1–4.25 [31].

intercalated cells, characterized by the luminal expression of the chloride/bicarbonate exchanger pendrin. Pendrin activity is driven by H^+-ATPases and may serve both bicarbonate excretion and chloride reabsorption. The activity and expression of pendrin is regulated by different factors including acid–base status, chloride delivery, and angiotensin II with a role in NaCl retention and blood pressure regulation [41]. Recently, a new mechanism of apical NaCl uptake was reported in the collecting duct, that results from parallel operation of 2 bicarbonate transporters: the Na^+ driven Cl^-/HCO_3^- exchanger NDCBE and the Na^+-independent anion exchanger pendrin [42].

Aldosterone acts primarily in the distal nephron to increase the reabsorption of Na^+ and Cl^- and the secretion of K^+ and H^+. Aldosterone deficiency, resistance or inhibition (Table 2) may result in hyperkalaemic, hyperchloraemic acidosis, also known as type IV renal tubular acidosis (RTA). There is also a very common and clinically important association of hyperchloremia (commonly mild hyperchloremic acidosis) with the so called hyporeninemic hypoaldosteronism. Hyporeninemic hypoaldosteronism is the most common cause of type IV RTA. Patients with this disorder are usually older diabetics and exhibit mild renal insufficiency (Table 2) [43]. The primary sites of action of aldosterone are in the connecting segment and the collecting tubules. Aldosterone promotes the reabsorption of NaCl and the secretion of K^+ in the distal tubulus and in the cortical collecting tubule, by increasing the number of Na^+-Cl^- cotransporters in the luminal membrane [44–47]. Hyporeninemia and hypertension could be explained by enhanced tubular reabsorption of chloride, which, by decreasing the lumen negative transepithelial potential ordinarily opposing sodium reabsorption, facilitated reabsorption of sodium, leading to extracellular volume expansion, hypertension, and hyporeninemia [26,29,33]. Hyporeninemia also might be explained if increased chloride reabsorption was occurring in the macula densa and suppressing renin stimulation directly [26–28,30].

Chloride excretion is an important mechanism in the kidney's adaptation to metabolic acidosis and chronic respiratory acid–base disturbances. In metabolic acidosis, the kidneys increase net acid excretion -primarily by enhanced ammonium chloride (NH_4Cl) excretion-, reaching a maximum after 3 to 5 days. The increase in chloride ion excretion without an associated increase in sodium ion excretion increases plasma strong ion difference (SID) and returns [HCO_3^-] and pH towards normal [48].

7. Hypochloremia

Many clinical situations are related to hypochloremia (Table 1). Chloride has an inverse relationship with bicarbonate. When serum chloride levels falls, due to gastrointestinal or renal loss, bicarbonate

Table 1
Conditions associated with hypochloraemia.

Chloride loss
Gastrointestinal chloride loss
Vomiting, nasogastric drainage
Some villous adenomas
Congenital chloridorrhea
High-volume ileostomy drainage
Renal losses
Chloruretic drugs
Bartter syndrome
Gitelman syndrome
Chronic respiratory acidosis
Hyperadrenocorticoism
Water gain in excess of chloride
Congestive cardiac failure
Syndrome of inappropriate ADH secretion
Excessive infusion of hypotonic solutions
Excessive gain of sodium relative to chloride
Sodium bicarbonate

reabsorption often increases proportionally, resulting in metabolic alkalosis. The most common gastrointestinal causes of hypochloremia are vomiting and nasogastric suctioning.

Renal loss of chloride can be caused by prolonged diuretic therapy, renal failure, and chloriduria. Excessive excretion of chloride in the urine is also seen in patients with Bartter's syndrome and hyperactivity of the renin-angiotensin aldosterone system. The interindividual distal tubular response to aldosterone activity seems to be dependent on the amount of chloride load available for the paracellular transtubular diffusion and from the ratio of apical K^+ channel expression to neutralize the transmembrane electronegativity induced by Na^+ transport [49]. Renal chloride loss may be secondary to chronic respiratory acidosis when bicarbonate is reabsorbed in exchange for chloride. Other causes of hypochloremia include hyponatremia and hypokalemia because chloride passively follows both sodium and potassium. Patients with congestive heart failure also can present with hypochloremia caused by excessive fluid buildup in the body and subsequent dilution of chloride levels, usually associated with hyponatremia. Certain drugs, such as bicarbonate, loop diuretics, thiazide diuretics, or infusions of 5% dextrose in water, also can also cause hypochloremia. Physical signs and symptoms of hypochloremia usually are those of the concomitant metabolic alkalosis. Apathy, confusion, cardiac arrhythmias, and neuromuscular irritability (related in part, perhaps, to a low ionized plasma calcium) are common when alkalosis is severe [48–52].

Metabolic alkalosis in humans is classically described as “chloride responsive” or “chloride resistant”, reflecting the possibility either to correct the metabolic alkalosis by the administration of NaCl or potassium chloride (KCl), or be resistant to this therapy [50]. Despite this nomenclature, suggestive of repletion with only chloride, one should realize that chloride is administered in general with either sodium and water, or potassium. Chloride responsive metabolic alkalosis is usually secondary to vomiting, diuretics, or incomplete or delayed recovery from hypercapnic acidosis and accounts for at least 80% of metabolic alkalosis cases. The normal kidney is highly efficient at excreting large amounts of HCO_3^- and accordingly, the generation of metabolic alkalosis requires both an increase in alkali and impairment in renal HCO_3^- excretion [51]. By evaluating the urine chloride concentration, one can distinguish between chloride responsive and chloride resistant metabolic alkalosis. If the kidneys perceive a reduced “effective circulating volume” they avidly reabsorb filtered Na^+, HCO_3^- and chloride through an activated renin-angiotensin-aldosteron system, thus reducing urine chloride concentration. Although gastric acid loss and diuretics may cause volume depletion and secondary alkalosis, chloride repletion (either in the form of NaCl or KCl) will correct the metabolic alkalosis, even if volume depletion persists [50]. Chloride depletion prevents bicarbonate secretion in the cortical collecting duct and increased bicarbonate reabsorption in the outer medullary collecting duct maintains chloride responsive alkalosis. Administration of chloride would increase chloride delivery to the collecting duct and increase urinary bicarbonate excretion by enhancing its secretion and diminishing its reabsorption [50]. Chloride resistant metabolic alkalosis largely compromises syndromes marked by absolute or apparent mineralocorticoid excess, but an important exception is active diuretic use that disables compensatory renal chloride retention [52].

8. Hyperchloremia (Table 2)

Metabolic acidosis caused by a gastrointestinal or renal loss of bicarbonate often results in a proportionally increase of chloride. A common cause of hyperchloremia is severe diarrhea with a loss of bicarbonate in the stool and subsequent rise in chloride. Other causes include extracellular fluid volume depletion, resulting in an increase in chloride and sodium concentration; urinary diversion into the sigmoid colon, where bicarbonate is secreted into the colon in exchange for reabsorption of urinary chloride; and pancreatic and biliary fistulas. Excessive administration of NaCl [53], CaCl or NH_4Cl [54] also can cause hyperchloremia. Medications that can contribute to hyperchloremia include cortisone preparations as sodium retention results in an accompanying rise in chloride. Other medications, such as acetazolamide, which promotes excretion of bicarbonate, and triamterene, which inhibits the secretion of hydrogen ions by the distal tubule, also can cause hyperchloremia. Metabolic acidosis is often classified by the anion-gap. Anion gap acidosis is caused by increased levels of organic acids (lactic and ketone acids) but also sulfates, phosphates and proteins may play a role in this respect. The anion gap remains

Table 2
Conditions associated with hyperchloraemia.

Chloride infusion
Administration of chloride-rich fluids, e.g. Sodium 0.9%, albumin, NH4CL, arginine HCL, lysine HCL, total parenteral nutrition
Water loss (either pure water loss or in excess of chloride loss)
Skin losses:
Exercise, severe dehydration
Fever
Hypermetabolic states
Extrarenal loss
Diarrhea
Burns
Renal loss
Central diabetes insipidus
Nephrogenic diabetes insipidus
Osmotic diuresis
Post-obstructive diuresis
Intrinsic renal disease
Diuretics
Definite or relative increase in tubular chloride reabsorption
Renal tubular acidosis
Early renal failure
Acetazolamide
Ureteral diversion procedures
Post hypocapnia
Miscellaneous
Bromide intoxication (false increase chloride concentration in assays that use ion electrode machines) [63]
Hyperchloremic acidosis
Carbonic anhydrase inhibitors
Small bowel diarrhea
Uretreral diversion procedures
Administration of acidic salts (NH4CL, arginine HCL, lysine HCL)
Early renal failure
Primary hyperparathyroidism
(Pseudo) hyperaldosteronism
Renal tubular acidosis

Common causes of type IV renal tubular acidosis

Aldosterone deficiency	Aldosterone resistance
Addisons disease	Obstructive uropathy
21-hydroxylase deficiency	Sickle cell nephropathy
Hyporeninemia	Amyloidosis
Diabetic nephropathy	Diabetic nephropathy
AIDS	Lupus nephritis
Tubulointerstitial disease	Pseudohypoaldosteronism
IgM monoclonal gammopathy	
NSAIDS	
Aldosterone inhibition	Drugs that interfere with tubular Na^+ channel function
Spironolactone	Amiloride
Analgesics	Triamterene
Cyclooxygenase inhibitors	Trimethoprim
Heparin	Pentamidine
Lovenox	

Drugs that interfere with basolateral Na^+/K^+-ATPase
Cyclosporine and tacrolimus

normal in metabolic acidosis when the decrease in bicarbonate concentration is replaced by chloride resulting in "hyperchloremic metabolic acidosis" or "normal anion gap acidosis.

9. Hyperchloremia and acidosis due to fluid resuscitation

A special focus on hyperchloremia and acidosis due to fluid resuscitation is necessary, not only because of the high incidence, but also because it is often unrecognized and poorly managed. Chloride rich solutions, such as 0.9% saline or albumin, used in large volumes can potentiate metabolic acidosis regardless of the underlying disease process [53,55]. While the serum chloride is usually below 110 mmol/L, the concentration of chloride in 0.9% saline is 154 mmol/L and that of human albumin solution up to 160 mmol/L [56]. Currently, there are two explanations for the pathophysiology of hyperchloremic metabolic acidosis due to fluid resuscitation [57–69]. To understand these explanations, one should be familiar with the two most used definitions about acids and bases. According to the Brønsted–Lowry definition acids are proton-donors and therefore chloride is a base [57], e.g. as the conjugate base of hydrochloric acid (HCl). Likewise, hyperchloremia causes acidosis indirectly as the stoichiometric relationship with bicarbonate will reduce the [HCO_3^-] resulting in metabolic acidosis to remain electroneutrality. In the dilutional explanation a reduction in the plasma bicarbonate concentration will occur when non-bicarbonate containing fluids are infused intravenously with a chloride concentration higher than plasma. According to Brønsted–Lowry, chloride is not an acid indicating that "hyperchloremic acidosis" and "hypochloremic alkalosis" are incorrect and misleading terms [58]. Dilutional acidosis and contraction alkalosis, however, are complex acid–base disorders resulting from changes in bicarbonate concentration in combination with changes in the concentration of weak plasma acids and buffering reactions. Therefore, the bicarbonate concentration may not change to the same degree as the magnitude of contraction or dilution [59].

According to the Arrhenius concept currently represented by the physicochemical approach pioneered by Peter Stewart, acids are substances that increase the [H^+] and likewise chloride is regarded as an acid because hyperchloremia will decrease the strong ion difference (SID), in particular the difference between sodium and chloride [62,63]. A lower SID will increase the [H^+], causing acidosis. The administration of large quantities of normal saline with a SID of zero will progressively lower the plasma SID of 40–42 mEq/L, producing hyperchloraemic metabolic acidosis. The infusion of Ringers lactate with a much lower chloride concentration than normal saline (109 mEq/L vs 154 mEq/L) and a SID of 28 mmol/l, would not decrease the pH [60–63]. This Stewart concept is increasingly popular among intensivists, but is still not adopted by the majority of physicians. Interestingly, although post-saline acidosis was first recognized in 1923 [64], there still is no common opinion about its pathogenesis [65–67].

Regardless of the used definition, the terms "hyperchloremic acidosis" and "hypochloremic alkalosis" may be deceiving, because acidosis as well as alkalosis may occur with both hypochloremia and hyperchloremia [2,58]. This highlights the importance of the chloride concentration, relative to sodium rather than absolute chloremia [2]. Therefore, one can also use the Cl:Na ratio to determine the cause of metabolic acidosis. A value of <0.75 is suggestive of a high anion gap acidosis and a value >0.79 is suggestive of a normal anion gap acidosis. Values in between may be seen in acidosis because of dual pathologies [56].

Currently we do not know if the metabolic acidosis that occurs from resuscitation with saline is deleterious to the patient [68,69]. However, although the data are still sparse, there is mounting evidence that the administration of unbalanced fluids in sufficient quantities may cause hyperchloremia with immune activation and inflammation [63], abdominal pain, increased risk of abdominal compartment syndrome, decreased splanchnic perfusion [58], renal dysfunction, a longer time to first urination, possibly, clotting abnormalities [63,66,67], and perhaps even increased mortality [58,68]. Chloride induced renal vasoconstriction and a fall in the glomerular filtration rate [70,71] may be the reason why a longer time to first micturition was observed with saline compared with a lactated solution in a crossover trial with human volunteers [2,72]. As normal saline is probably the most commonly prescribed fluid worldwide, this may be a significant issue, but presently there is insufficient data to advocate against its use or to switch to balanced solutions like Ringers in all cases of high volume resuscitation. Another important issue may be that this saline induced hyperchloremic acidosis can be misinterpreted by inexperienced physicians. Recognition of this entity may prevent unnecessary and potentially harmful prolonged resuscitation [73]. As an example, despite correction of hypoxia, hypovolemia or ketoacidosis [55], ongoing metabolic acidosis related to hyperchloremia and decreased bicarbonate may be misdiagnosed as being due to inadequate perfusion rather than the overzealous saline treatment and may encourage the clinician to prolong the aggressive resuscitation period. This could involve either saline administration, which may perpetuate the acidosis, or excessive use of inotropic agents, which may drive a lactic acidosis through anaerobic glycolysis [74], increase oxygen consumption due to thermogenesis [75], provoke arrhythmias [76], and produce other harmful metabolic effects [73]. Other common examples are further administration of saline-based fluids, less permissive hyperventilation in case of low pH values [77], and extended treatment of diabetic ketoacidosis [77,78].

10. Chloride as a diagnostic tool

Chloride can serve as an important component of diagnostic tests in many clinical situations. In these cases, chloride can be tested in sweat, serum, urine and feces. Cystic fibrosis is associated with a sweat chloride concentration above 60 mmol/l [79]. In normotensive patients with hypokalemia and alkalosis a high urine chloride concentration may differentiate several disorders. The chloride concentration will then be high in magnesium deficiency, Bartter syndrome, Gitelman syndrome and when diuretics are used and a low urine chloride concentration will then be found in case of vomiting and the use of high dosages of sodium containing penicillin's [2,49–52]. In the assessment of acid–base and osmolal disorders, serum and urine chloride measurement is essential for commonly used formulas including the anion gap, the strong anion gap, the strong ion difference, chloride/sodium ratio [54], and the urine sodium excretion (Table 3) [80,81]. While chloride needs to be taken into account to correctly to diagnose particular electrolyte disorders, however, in several "standard situations" it may still be easier to look at Na^+ or K^+ and water rather than Cl^-.

Urine analysis has not received great attention in critically ill patients, likely due to the common practice of only analyzing 24-hour collected specimens. A novel analyzer named Kidney INstant monitorinG (K.IN.G), was developed to allow non-invasive, quasi-continuous analysis of urine pH, sodium, chloride, potassium and ammonium levels. The K.IN.G analyzer, allowing quasi-continuous monitoring of urinary pH and principal electrolyte levels, may represent a novel tool for clinical and research purposes that may increase our knowledge of the role of chloride in health and disease [82].

11. Conclusion

Chloride is one of the most important electrolytes in blood. After sodium, chloride is the most abundant electrolyte in serum, with a key role in the regulation of body fluids, electrolyte balance, the preservation of electrical neutrality, acid–base status and it is an essential component for the assessment of many pathological conditions. When assessing serum electrolytes, abnormal chloride levels alone

Table 3
Chloride as an aid in diagnosing clinical disorders.

	Indication	Interpretation
Serum chloride		
Anion gap: $[Na^+] - [Cl^-] - [HCO_3^-]$	Acid–base disturbances, in particular metabolic acidosis	High: metabolic acidosis due to acid (e.g. lactate, ketoacids) Normal: e.g. metabolic acidosis due to fluid resuscitation, diarrhea, renal tubular acidosis Low: bromide, iodine [84], paraprotein
Strong ion difference (SID)	Acid–base disturbances	Decreased in metabolic acidosis Increased in metabolic alkalosis
Strong anion gap	Acid–base disturbances, in particular metabolic acidosis	High: metabolic acidosis due to acid (e.g. lactate, ketoacids) Normal: e.g. metabolic acidosis due to fluid resuscitation, diarrhea, renal tubular acidosis
CL/Na ratio	Acid–base disturbances, in particular metabolic acidosis	In metabolic acidosis [56] < 0.75 high anion gap > 0.79 normal anion gap
CL/P ratio	Hypercalcemia	> 103 hyperparathyreoidism [83]
Chloride in sweat	Cystic fibrosis	sweat chloride > 60 mmol/L [79]

Urine tests				
	Hypovolemia	Vomiting	$[Na^+]$	$[Cl^-]$
		Recent	high	low
		Remote	low	low
		Diuretics		
		Recent	High	High
		Remote	Low	Low
		Diarrhea	Low	High
		Bartter's or Gitelmans's Syndrome	High	High
Urine anion gap $[Na^+] + [K^+] - [Cl^-]$	Normal anion gap acidosis	Negative = normal Positive = renal tubular acidosis type 1 and 4		
Urine osmolal gap $Na^+ + K^+$ [urea nitrogen in mg/dL]/2.8 + [glucose in mg/dL]/18	Normal anion gap acidosis	< 40 mEq/L than measured urine osmolality indicates impairment in NH_4^+ excretion		
Spot urine $[Cl^-]$	Metabolic alkalosis	< 25 = chloride responsive[#] > 40 = chloride resistant[*]		
Spot urine dipstick chloride/creatinine ratio	Sodium excretion			
Fecal chloride	Congenital chloridorhea Some forms of villous adenoma	> 16 mmol/l		

Form of metabolic alkalosis responsive [#] or resistant[*] to sodium chloride therapy.

usually signify a more serious underlying metabolic disorder, such as metabolic acidosis or alkalosis. This prominent role, without any doubt, justifies its classification as "the queen of electrolytes." Despite its importance, we tend not to give chloride the importance we give to most cations probably because, in contrast to many cations, it is difficult relate symptoms exclusively to abnormal chloride concentrations. "Majestic" recognition may, however, become closer in the near future, perhaps with the help of "the K.IN.G" [82].

Chloride learning points

Concerning

- Chloride is the principal anion in the extracellular fluid and it is the second main contributor to plasma tonicity. Chloride also has a key role in the regulation of body fluids, electrolyte balance, the preservation of electrical neutrality, acid–base status.
- Abnormal chloride levels alone usually signify a more serious underlying metabolic disorder, such as metabolic acidosis or alkalosis.
- Abnormalities in chloride channel expression and function in many organs can cause a wide range of disorders.
- Chloride is an important component of diagnostic tests in a many clinical situations.
- Normal saline produces hyperchloremic metabolic acidosis

Conflict of interest statement

We have no conflict of interest.

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