Investigative algorithms for disorders affecting plasma chloride: a narrative review

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Background and Objective: The following article is part of a special series to aid the reader in diagnosing the cause of various electrolyte imbalances. A focussed literature review will, by the end of this article, enable the reader to correctly order and interpret laboratory tests to investigate derangements in plasma chloride.

Methods: A narrative, focused literature review was performed of English language resources using PubMed, OMIM and Google. References published from database inception to January 2022 were searched for during September 2021 to January 2022. Further articles were identified from reference lists.

Key Content and Findings: Chloride concentration can be affected by changes in acid base status and is closely linked to sodium homeostasis. Hyperchloraemia is most commonly due to water loss and associated with hypernatraemia, mismatch may indicate a spurious result. Hypochloraemia is associated with metabolic alkalosis and renal salt-losing tubulopathies. Although 24-hour urine chloride collections can be used to aid diagnosis the range of variables affecting results makes it controversial and results should only be interpreted with caution.

Conclusions: Diagnostic schema will be presented, and the limitations of the laboratory tests discussed. By provision of diagnostic algorithms investigation choice and interpretation is supported allowing healthcare professionals to confirm clinical diagnoses and more expertly review the most complex cases.

Keywords: Chloride; hyperchloraemia; hypochloraemia; investigation; algorithm

Introduction

Chloride is the major extracellular anion, with a concentration of approximately 100–108 mmol/L found in plasma (method dependent), 70 mmol/L in red blood cells, and only 2 mmol/L in skeletal muscle. Despite accounting for 70% of the negative ion content of the body, chloride ions are frequently overlooked in clinical chemistry with abnormalities accounting for/occurring in up to 40% of

hospital admissions, and if not controlled, can worsen prognosis and increase mortality (1,2). The measurement of plasma chloride is needed to calculate the anion gap, and can help diagnose non-respiratory acidosis, as well as chloride-losing diseases. In patients receiving intravenous chloride containing fluids (i.e., normal saline), measurement of chloride is essential when querying excessive intake which if undiagnosed can be fatal (3). Chloride concentration however usually mirrors sodium, except in hypochloraemic

Table 1 The search strategy summary

Items	Specification
Date of search (specified to date, month and year)	September 2021 to January 2022
Databases and other sources searched	Medline, Google Scholar, OMIM
Search terms used (including MeSH and free text search terms and filters). Examples include:	Chloride, Hypochloraemia (emia), Hyperchloraemia (emia), Diagnosis, Investigation, Causes, Aetiology, Paediatrics, Pregnancy
Timeframe	From database inception to January 2022
Inclusion and exclusion criteria (study type, language restrictions, etc.)	All papers and reviews were included restricted to English
Selection process (who conducted the selection, whether it was conducted independently, how consensus was obtained, etc.)	C Darragh-Hickey and KE Shipman conducted initial search, with refinement by all other authors to obtain consensus and agreement
Any additional considerations, if applicable	Seminal texts were also searched and the references of important articles and texts were obtained and checked for relevance

alkalosis and hyperchloraemic acidosis, and depends also on the water content of the extracellular compartment. The functions of chloride ions include maintaining acid-base homeostasis along with bicarbonate, regulating osmolarity, maintaining electroneutrality, as well as producing gastric hydrochloric acid (1).

Diagnostic algorithms will be presented to provide a possible approach to investigate abnormalities of plasma chloride focusing on the role of the laboratory tests. This article is not meant to replace current guidelines and reviews, nor replace thorough clinical assessment. Instead, these algorithms are aimed to enhance the understanding of the role of diagnostics in the clinical pathway, particularly as the healthcare team expands to include many professionals who may have had less training or exposure to both selecting and interpreting investigations. Quality and efficiency of patient care is promoted by the appropriate use of diagnostics. We present the following article in accordance with the Narrative Review reporting checklist (available at https://jlpm.amegroups.com/article/view/10.21037/jlpm-22-7/rc).

Methods

The narrative literature review was created by searching Medline, Google Scholar, OMIM and seminal texts. Synthesis of the information inspired the creation of the diagnostic algorithms with the limitation to try and ensure tests recommended would be available to most laboratory users. The literature was searched over the period September 2021 to January 2021. The language was restricted to English. For further information please see supplementary information (*Table 1*).

Chloride metabolism

Dietary chloride is primarily absorbed along the whole length of the intestinal tract complexed with sodium as salt (*Figure 1*). Chloride's role is mostly dependent on sodium. Therefore, understanding sodium homeostasis provides insight into chloride regulation (see the sodium article within this series). Conversely, if the chloride concentration is not proportional to the sodium concentration, this can indicate a possibly spurious result. The average daily consumption is difficult to estimate as salt intakes and needs vary so widely across the world. Chloride malnutrition is rare, and it is more likely that we all generally consume too much (4). The recommended maximum limit of chloride consumption is 2.3 g/day (65 mmol/day) but can range from 5.8 to 11.8 g/day (160–330 mmol/day) (3,5).

Chloride is absorbed almost completely by the gastrointestinal tract primarily passively through a paracellular pathway in the small intestine, driven by amino acids and glucose absorption. Members of the *SLC26* and *SLC4* gene families provide many of the channels and transporters involved in chloride transcellular flux. Transporters include the anion Cl^-/HCO_3^- exchanger in the ileum and colon, parallel Cl^-/HCO_3^- and Na^+/H^+ exchangers, and the basolateral Na^+-K^+-$2Cl^-$ cotransporter (NKCC) (6). The parallel exchangers function following the production of HCO_3^- and H^+ from carbonic anhydrase, and H^+ exits through the Na^+/H^+ exchanger-3 (NHE3).
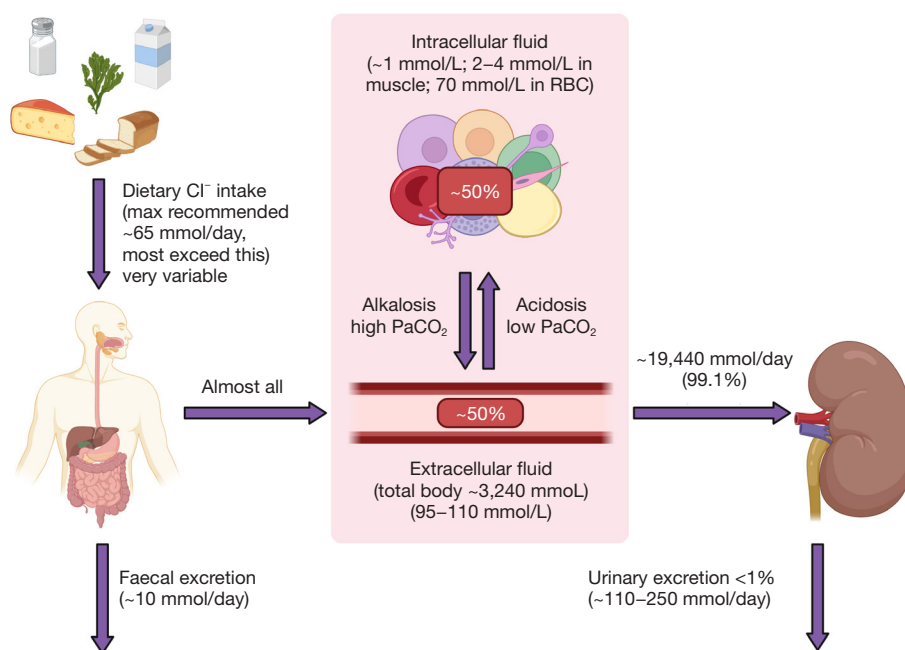
Figure 1 An overview of chloride distribution in the human body. Chloride intake is variable and dietary dependent. Some chloride is lost in the faeces with the majority passing into the extracellular and intracellular fluid. Acidosis, or a low $PaCO_2$, cause a shift of chloride ions from the extracellular fluid into the intracellular fluid. Conversely, alkalosis or a high $PaCO_2$ cause chloride ions to shift from the intracellular fluid into the extracellular fluid. Chloride is freely filtered and reabsorbed at the kidney, with <1% excreted in the urine. $PaCO_2$, carbon dioxide partial pressure; RBC, red blood cell.

Hydrogen and bicarbonate ions are swapped for Na^+ and Cl^- ions. Importantly, chloride excretion into the gut lumen is the main driving force for fluid flux into the gastrointestinal tract (4). Excretion is via the cystic fibrosis transmembrane conductance regulator (CFTR), the chloride type-2 channel (ClC-2) and calcium-activated Cl^- channels (CaCC) (4).

Chloride is freely filtered at the renal glomeruli (*Figure 2*), and 60% is reabsorbed in the proximal tubule paracellularly and through the apical chloride anion Cl^-/HCO_3^- exchanger (4). This anion exchanger also absorbs bicarbonate, glucose, phosphate, and other anions (anions such as bicarbonate, formate and oxalate) (4). At the thick ascending loop of Henle, a NKCC facilitates chloride reabsorption (7). Chloride then exits the cell through the basolateral chloride channel. A sodium-chloride channel (NCC) in the distal convoluted tubule also facilitates chloride reabsorption (6). Finally, at the collecting duct, the total urinary chloride concentration is determined. Here, chloride is reabsorbed paracellularly in response to a negative lumen potential created by epithelial sodium channels (ENaC) directing sodium intracellularly. Furthermore, a chloride-bicarbonate transporter (pendrin), also facilitates chloride reabsorption (8).

Chloride concentration is high in red blood cells (70 mmol/L). A 'chloride shift' (exchange for bicarbonate) is important for acid-base balance and carbon dioxide transport, given that CO_2 is mostly carried as carbonic acid and converted to bicarbonate ions (6). Acid-base status greatly affects chloride homeostasis as renal bicarbonate reabsorption will stimulate chloride loss in the kidney to help maintain electroneutrality. Conversely, excessive renal chloride loss can cause a metabolic alkalosis due to this bicarbonate exchange (6). An increase in aldosterone secretion, which drives potassium and hydrogen ion loss, will also drive a hypochloraemic metabolic alkalosis (however depending on other factors, e.g., chloride delivery to the tubule and potassium channel expression, aldosterone can also lead to salt retention and hence hyperchloraemia). Hypokalaemia itself also stimulates hydrogen ion loss and a metabolic alkalosis hence hypochloraemia with hypokalaemia.
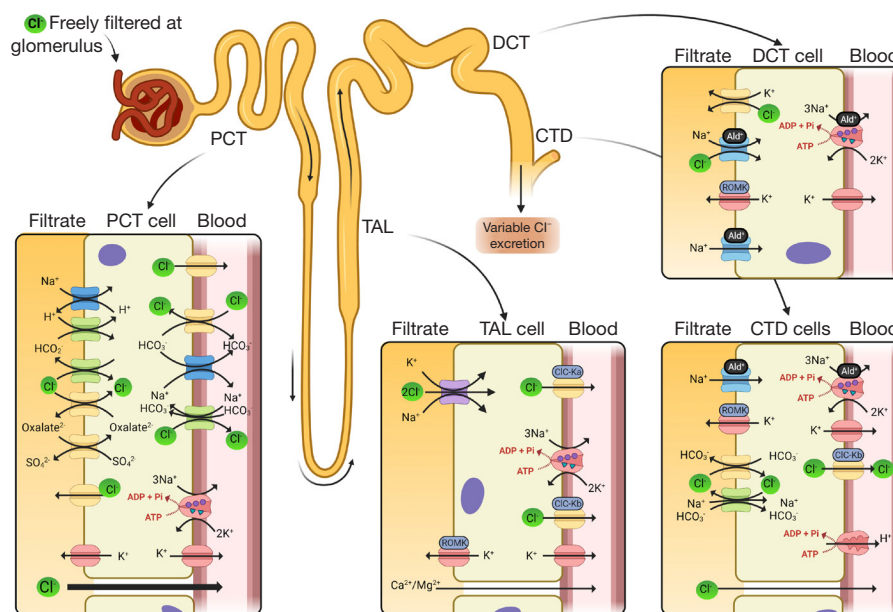
Figure 2 Renal handling of chloride in humans. Chloride (highlighted in green) is freely filtered at the nephron and 60% is reabsorbed in the PCT through a chloride anion exchanger and paracellularly. At the TAL, an NKCC reabsorbs chloride. At the DCT, chloride is reabsorbed through an NCC. Paracellular chloride absorption occurs at the collecting duct as well as transport using a chloride-bicarbonate transporter. ADP, adenosine diphosphate; ALD, aldosterone; ATP, adenosine triphosphate; ClC-Ka/b, chloride channel Ka or Kb; DCT, distal convoluted tubule; NCC, sodium-chloride channel; NKCC, Na$^+$-K$^+$-2Cl$^-$ cotransporter; PCT, proximal convoluted tubule; Pi, inorganic phosphate; ROMK, renal outer medullary potassium channel; TAL, thick ascending loop of Henle.

It is important to note that methods for chloride quantitation vary. This will affect both reference intervals but importantly calculations, such as anion gap, meaning that the anion gap may be positive or negative depending on method rather than real status (4). Measurement of random urine chloride collections is not recommended due to large inter-individual variation, and therefore several 24-hour collections are preferred to estimate renal losses more accurately (3). Even in abnormal chloride states, where a random collection might normally suffice, it is important to note that other factors, e.g., acid-base status, chloride load to the kidney and potassium channel expression, may affect excretion and therefore caution is required with interpretation (4). In fact, urinary chloride concentrations are not used widely to identify the cause of chloride dysregulation.

Hypochloraemia

In most cases, hypochloraemia (plasma chloride <100 mmol/L) is accompanied by hyponatraemia (unless acid-base disturbance

is present, see below). Therefore, sodium pathways are useful when investigating abnormalities of chloride (see sodium article in this series). Here, we present an algorithm for investigating hypochloraemia (*Figures 3*).

The combined picture of blood tests with clinical assessment may clearly establish the cause, but if the hypochloraemia is unexpected and defying immediate diagnosis, then it is worth initially deciding if the value is true or spurious. Plasma chloride is quantitated using ion specific electrodes. Like sodium, pseudohypochloraemia can occur when measuring chloride using indirect ion specific electrodes in patients with nonaqueous contaminants, such as hyperlipidaemia, or hyperproteinaemia in multiple myeloma (for a more in-depth explanation please see sodium article within this series and *Figure 3*) (9).

Lack of dietary sodium chloride intake is very rare but diet and drug history should be reviewed carefully. Identify medications which may put the person at risk of renal or gastrointestinal losses, haemodilution or metabolic alkalosis (e.g., steroids). It is rare to see patients with hypochloraemia and hypernatraemia, and this usually indicates excess
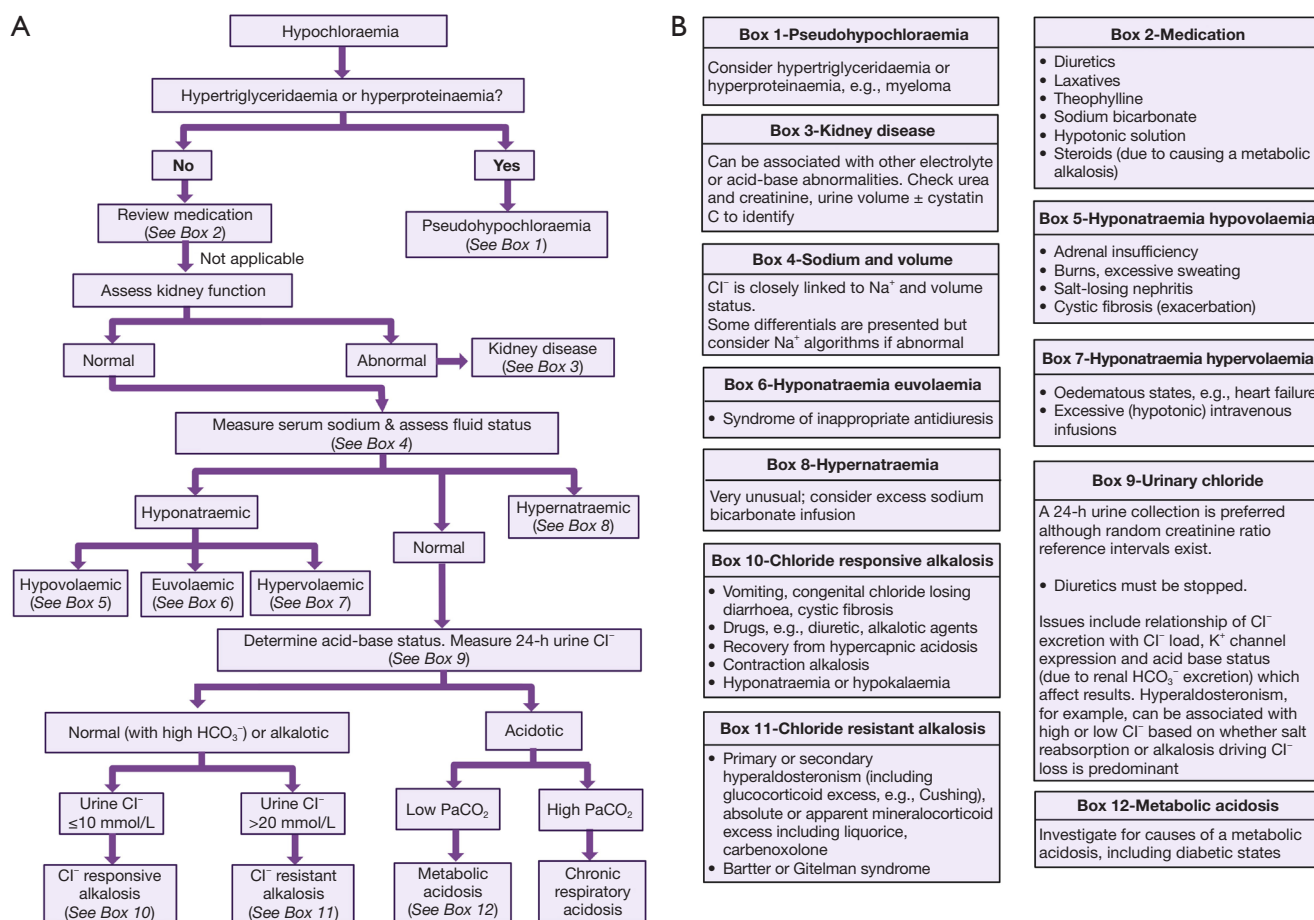
Figure 3 Diagnostic laboratory algorithm for hypochloraemia in humans (A) with additional supportive information (B). (A) Diagnostic laboratory algorithm for hypochloraemia in humans. (B) Boxes providing supportive information for diagnostic algorithm in (A). $PaCO_2$, carbon dioxide partial pressure.

sodium bicarbonate infusion or sample contamination with sodium citrate.

The next stop is to consider renal function and particularly salt-losing nephropathies (10) and the fluid status of the patient. Good renal function is essential for chloride (and sodium) reabsorption. Acute or chronic renal disease can reduce chloride reabsorption and lead to hypochloraemia but particularly those diseases affecting renal tubular function. The quickest and simplest method to assess renal function is to measure the serum/plasma creatinine concentration and monitor the urine output (11). Chronic kidney disease (CKD) can also be detected via urine albumin or sediment abnormalities and electrolyte disturbances due to a tubular disorder (12). Urea and cystatin C are alternative biomarkers to assess renal function, however, cystatin C is not measured routinely

albeit independent of muscle mass, and urea has its own disadvantages. Improving renal function will often improve chloride status.

Loss of volume and other electrolytes e.g., hyponatraemic hypovolaemic hypochloraemia may suggest salt-losing nephropathy (or losses via skin for example) however endocrine causes, such as adrenal insufficiency, should also be considered. Presence of glucose, phosphate and protein (or amino acids) in the urine may help indicate the presence of a renal tubular cause if not evident clinically (13). Hyponatraemia can also indicate haemodilution. Importantly therefore, if euvolaemic, consider syndrome of inappropriate antidiuresis and if hypervolaemic, consider failure states, e.g., congestive cardiac failure or excessive hypotonic infusions.

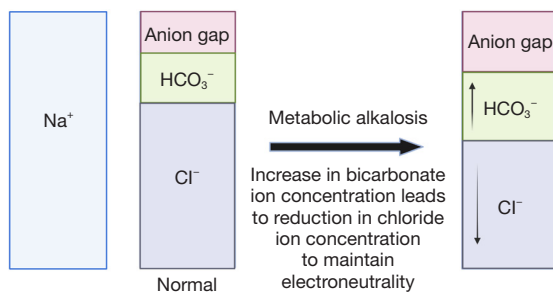The final part of the algorithm focuses on examining the

Figure 4 Relation between major anions and cations in normal physiology and metabolic alkalosis. Normal physiological ratios of sodium (green), chloride (yellow) and bicarbonate (blue) in the blood. The normal anion gap is shown (red). During metabolic alkalosis, bicarbonate ions are increased and chloride is decreased to maintain electroneutrality. Plasma proteins also become increasingly negatively charged which slightly raises the anion gap. Conversely, if plasma chloride is lost, bicarbonate ions are upregulated to compensate for the loss causing a metabolic alkalosis.

acid-base status as disturbances can cause hypochloraemia with a normal plasma sodium concentration (see acidosis and alkalosis articles in the same series of articles). In health, the concentration ratio of sodium:chloride is 1.4:1. However, this ratio is often skewed in acid-base conditions. Chloride depletion can cause metabolic alkalosis as bicarbonate ions are regenerated to maintain electroneutrality (please see alkalosis article in the series and *Figure 4*) (14). On the other hand, metabolic alkalosis can also cause hypochloraemia as bicarbonate is upregulated and chloride is purposely lost for maintenance of electroneutrality (14). In these disease states, H+ ions are lost from the body, and acid-base homeostasis must be restored by upregulating HCO_3^- regeneration in the kidney. The net effect is to increase chloride excretion (14).

A 24-hour urinary chloride is rarely performed as it is affected by many factors (see figure 3b box 9) and the use of specific diagnostic thresholds varies throughout the literature. However, it can aid the investigation of alkalosis (*Figures 3*) (12,15). Chloride responsive or resistant alkalosis refers to whether the condition can be reversed by saline or other chloride containing fluid replacement or not (*Figures 3A*) (see potassium and alkalosis articles in this series for further clarification on these differentials) (16). Low urine chloride (≤10 mmol/L) defines chloride responsive and includes causes such as volume depletion, diarrhoea and vomiting. Vomiting the gastric contents

with chloride concentrations of 100 mmol/L, and sodium 20–30 mmol/L, causes hypochloraemia (of around 80–90 mmol/L) and a slightly low sodium (~130 mmol/L). Plasma chloride concentrations can fall to 45–70 mmol/L in patients with bulimia, gastric outlet obstruction and in problem drinkers with chronic vomiting (8). Other causes of saline or chloride responsive alkalosis include alkalotic or diuretic drugs, hyponatraemia and hypokalaemia.

Chloride resistant alkalosis (urine chloride >20 mmol/L) can indicate endocrine or drug effects on chloride transport in the kidneys (hyperaldosteronism or carbenoxolone) or a tubulopathy. Gitelman and Bartter syndromes are examples of tubulopathies with the effect of diuretics on the fractional excretion of chloride, helping to distinguish Bartter from Gitelman syndrome or urine calcium:creatinine ratio, which is usually >0.2 in Bartter (<0.2 in Gitelman syndrome) with diminished urine concentrating ability, if access to genetic testing is not readily available (17). These syndromes are discussed in more detail in the alkalosis article within this special series.

Gitelman syndrome is characterised by hypokalemic metabolic alkalosis with hypocalciuria, and hypomagnesemia. It is autosomal recessive and caused by loss of function mutations in the thiazide sensitive sodium-chloride symporter (NCC) located in the distal convoluted tubule, hence is similar in presentation to thiazide use. A single mutation can result in a mild phenotype with fatigue and cramps. The differentials include vomiting especially bulimia, liquorice toxicity and Conn syndrome. Glycyrrhizin in liquorice inhibits 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2), which catalyses NAD+-dependent dehydrogenation of cortisol to cortisone in the renal tubules. The cortisol interacts with mineralocorticoid receptors in the tubules mimicking Conn syndrome. Genetic testing is becoming standard for many of these conditions rather than reliance on the biochemical phenotype; local discussion is recommended for such cases.

If acidosis is identified, then use the partial pressure of carbon dioxide to classify if respiratory or metabolic and investigate accordingly (please see acidosis article in this series). Acidosis should be rare but if the acidosis is chronic bicarbonate concentration may increase (and thereby chloride concentration falls).

Rare causes of hypochloraemia

A rare cause of hypochloraemic metabolic alkalosis is congenital chloride diarrhoea (CCD). CCD is caused by

defects in the Cl^-/HCO_3^- anion exchanger linked with mutations in the sulphate permease transporter *SLC26A3* gene. Normal faecal chloride concentration is 10–15 mmol/L. However, this can increase to 90 mmol/L in CCD but can be lower if very chloride deplete (18). Patients with CCD are alkalotic as HCO_3^- cannot get excreted (5). Cystic fibrosis (CF) is also linked with hyponatraemia and hypochloraemia, due to hyperaldosteronism with alkalosis to replace the salt lost in sweat (19,20). Both of these causes would appear in the hypovolaemic, hyponatraemic and chloride responsive areas of the algorithm.

Apparent mineralocorticoid excess (AME) syndrome occurs following a mutation in the *HSD11B2* gene encoding 11β-HSD2. Individuals with AME experience a hypokalaemic metabolic alkalosis with hypertension. AME mirrors glycyrrhizic acid/glycyrrhetinic acid found in liquorice, inhibiting the same enzyme, hence causing the same symptoms. Additionally, 11β-HSD2 is saturated in hypercortisolaemia, and this explains why Cushing, and ectopic ACTH secreting tumours, also cause metabolic alkalosis with hypokalaemia due to overactivation of the mineralocorticoid receptor. AME has two subtypes; the childhood form AME type I, which is severe and causes hypertension with failure to thrive, and the adult form AME type II which is much milder. When diagnosing AME, it is essential to analyse urine steroid profiles to confirm the enzyme deficiency and/or perform genetic testing. Blood pressure and renin aldosterone analysis help exclude Bartter syndrome from this differential diagnosis (21).

An example of another rare condition is Dent disease, an extremely rare x-linked disorder caused by mutations in the genes *CLCN5* (type 1) and *OCRL1* (type 2) and presents with features of a tubulopathy including proteinuria, hypercalciuria, nephrolithiasis and rickets (22). *CLCN5* encodes the chloride channel protein 5 (ClC-5) that exchange H^+ for Cl^- ions in the proximal tubule. A few patients can manifest hypochloraemia (and hypokalaemia) (23).

There are a variety of other congenital and acquired renal diseases affecting tubular function, but multiple abnormalities and age of onset may help one to identify these. Liddle syndrome is caused by activating mutations in ENaC genes *SCNN1A*, *SCNN1B*, *SCNN1G* which are regulated by aldosterone (24). Liddle patients normally presents in childhood with hypertension, hypochloraemia, hypokalaemia and metabolic alkalosis (25). Liddle syndrome can be confirmed genetically in patients with clinical evidence of primary hyperaldosteronism but with low renin activity and aldosterone concentration and normal urine steroid profile.

Hyperchloraemia

Hyperchloraemia (plasma chloride >110 mmol/L), usually coincides with hypernatraemia, and occurs when the body loses pure water (hypotonic fluid loss). This can occur through the skin (fever, burns, exercise, excess sweating, e.g., thyrotoxicosis and hypermetabolism), extrarenal (diarrhoea or drains) or renal systems (*Figure 5A,5B* and see sodium article in linked series). Otherwise, hyperchloraemia occurs when patients are administered excessive amounts of chloride containing saline solutions or chloride drugs (26). Knowledge of sodium, potassium, acid and base disturbances are required to determine causes (see linked articles in this series). Thorough clinical assessment and initial review of the bloods may be all that is required however for the experienced clinician however if no cause is obvious then the algorithm should aid elucidation of the cause.

The diagnostic algorithm starts with the rare but important possibility of pseudohyperchloraemia in the assumption that this cause will be less familiar to most laboratory users and further diagnostics should not be wasted in this setting. Pseudohyperchloraemia appears if electrode methods mistake other anions, e.g., bromide (from bromvalerylurea for example), iodide, thiocyanate, nitrate and salicylate (hence salicylate can give an unexpectedly low anion gap acidosis), for chloride (27-31). Acute bromide intoxication, from bromide medications, is rarely seen as bromide in the body causes vomiting and nausea preventing toxic accumulation. Chronic bromide intoxication from continuous intake more frequently occurs when intake exceeds renal excretion. Symptoms of toxicity occur with 19–25 mmol/L bromide (8).

Further review of the medication and intake is then warranted to include review of the constituents of any intravenous infusions, for example albumin infusions, and remember that steroids stimulate salt reabsorption in the kidney. Chloride toxicity can be also caused by saltwater drowning or saline abortion (9).

Following this, fluid status should then identify the commonest cause, as listed above, of water loss. It is worth noting that diarrhoea can cause unexpectedly significant hyperchloraemia for the volume lost as bicarbonate is also lost through the gut and chloride is maintained for electroneutrality maintenance (8). Diabetes insipidus should be suspected in the presence of polyuria and polydipsia and biochemically with hyperchloraemic hypernatraemia with
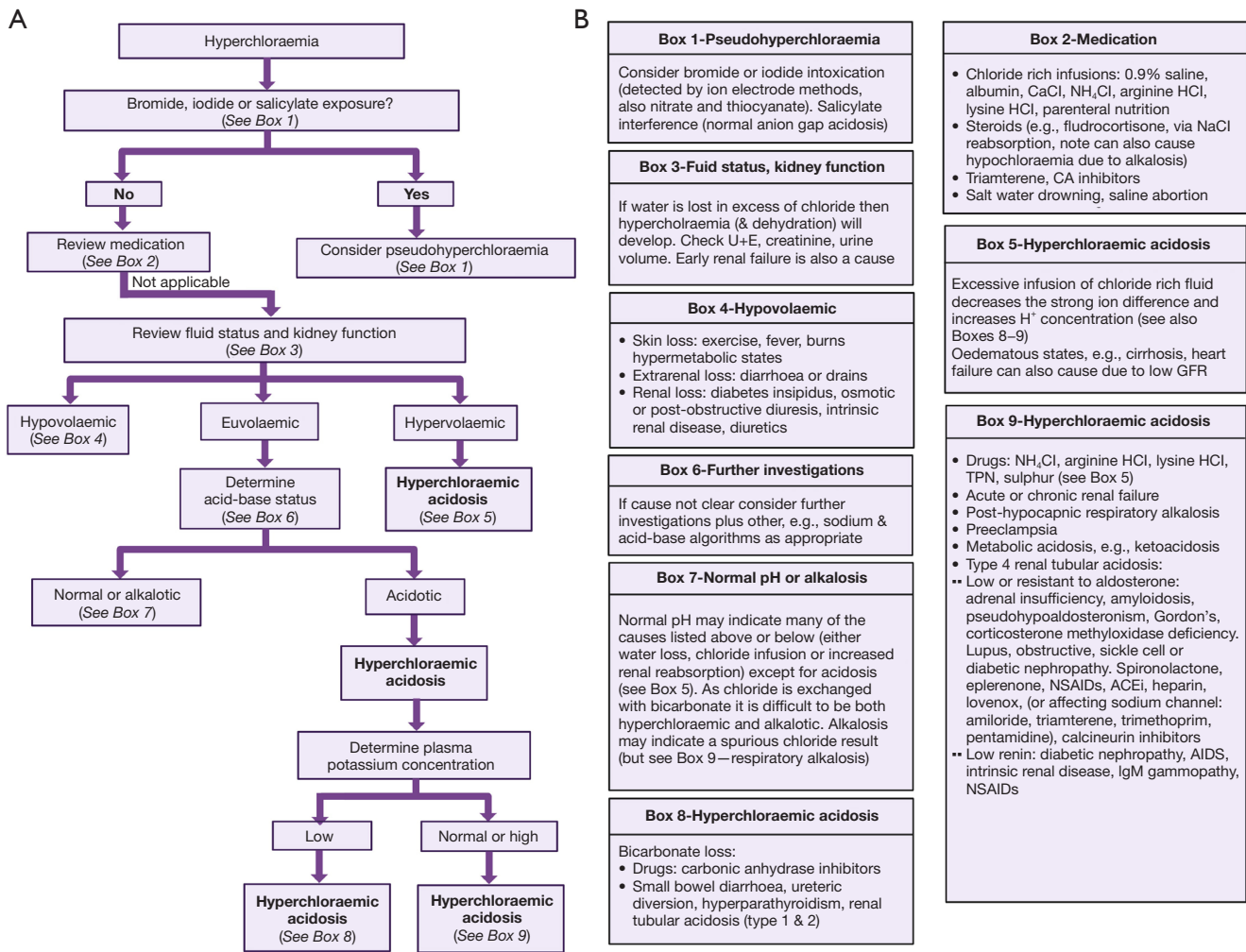
A

B

Box 1-Pseudohyperchloraemia

Consider bromide or iodide intoxication (detected by ion electrode methods, also nitrate and thiocyanate). Salicylate interference (normal anion gap acidosis)

Box 3-Fuid status, kidney function

If water is lost in excess of chloride then hypercholraemia (& dehydration) will develop. Check U+E, creatinine, urine volume. Early renal failure is also a cause

Box 4-Hypovolaemic

- Skin loss: exercise, fever, burns hypermetabolic states
- Extrarenal loss: diarrhoea or drains
- Renal loss: diabetes insipidus, osmotic or post-obstructive diuresis, intrinsic renal disease, diuretics

Box 6-Further investigations

If cause not clear consider further investigations plus other, e.g., sodium & acid-base algorithms as appropriate

Box 7-Normal pH or alkalosis

Normal pH may indicate many of the causes listed above or below (either water loss, chloride infusion or increased renal reabsorption) except for acidosis (see Box 5). As chloride is exchanged with bicarbonate it is difficult to be both hyperchloraemic and alkalotic. Alkalosis may indicate a spurious chloride result (but see Box 9—respiratory alkalosis)

Box 8-Hyperchloraemic acidosis

Bicarbonate loss:
- Drugs: carbonic anhydrase inhibitors
- Small bowel diarrhoea, ureteric diversion, hyperparathyroidism, renal tubular acidosis (type 1 & 2)

Box 2-Medication

- Chloride rich infusions: 0.9% saline, albumin, CaCl, NH$_4$Cl, arginine HCl, lysine HCl, parenteral nutrition
- Steroids (e.g., fludrocortisone, via NaCl reabsorption, note can also cause hypochloraemia due to alkalosis)
- Triamterene, CA inhibitors
- Salt water drowning, saline abortion

Box 5-Hyperchloraemic acidosis

Excessive infusion of chloride rich fluid decreases the strong ion difference and increases H$^+$ concentration (see also Boxes 8–9)
Oedematous states, e.g., cirrhosis, heart failure can also cause due to low GFR

Box 9-Hyperchloraemic acidosis

- Drugs: NH$_4$Cl, arginine HCl, lysine HCl, TPN, sulphur (see Box 5)
- Acute or chronic renal failure
- Post-hypocapnic respiratory alkalosis
- Preeclampsia
- Metabolic acidosis, e.g., ketoacidosis
- Type 4 renal tubular acidosis:
  - Low or resistant to aldosterone: adrenal insufficiency, amyloidosis, pseudohypoaldosteronism, Gordon's, corticosterone methyloxidase deficiency. Lupus, obstructive, sickle cell or diabetic nephropathy. Spironolactone, eplerenone, NSAIDs, ACEi, heparin, lovenox, (or affecting sodium channel: amiloride, triamterene, trimethoprim, pentamidine), calcineurin inhibitors
  - Low renin: diabetic nephropathy, AIDS, intrinsic renal disease, IgM gammopathy, NSAIDs

Figure 5 Diagnostic laboratory algorithm for hyperchloraemia in humans (A) with additional supportive information (B). (A) Diagnostic laboratory algorithm for hyperchloraemia in humans. (B) Boxes providing supportive information for diagnostic algorithm in (A). CA, carbonic anhydrase; U+E, urea and electrolytes; GFR, glomerular filtration rate; NSAIDs, nonsteroidal anti-inflammatory drugs; ACEi, angiotensin converting enzyme inhibitors; AIDS, acquired immunodeficiency syndrome.

a low urine osmolality e.g., 100 mOsm/L, and low urine chloride and sodium concentrations (8).

If patients are hypervolaemic with hyperchloraemia, consider chloride rich infusions which should have been apparent in the medication review (8). Finally, if the patient is euvolaemic then suspect that the driver for the hyperchloraemia is an acid base disturbance such as metabolic acidosis. Besides diarrhoea (bicarbonate loss and hyperaldosteronism), renal tubular acidosis (RTA) is an important cause which is effectively a renal tubular dysfunction preventing acid excretion or bicarbonate reabsorption; for further information on please see

linked article on acidosis. Pregnancy is also a cause of hyperchloraemic acidosis, as are other causes of metabolic acidosis. Alkalosis should be unusual as to maintain electroneutrality increasing bicarbonate concentration would reduce chloride ion concentration. Alkalosis therefore may suggest a spurious result as discussed above.

Rare causes of hyperchloraemia

A rare cause of hyperchloraemic metabolic acidosis, and hyperkalaemic hypertension, is Gordon syndrome (also known as pseudohypoaldosteronism type II). Mutations

occurring in either *WNK1*, *WNK4*, *KLHL3*, or *CUL3* cause accumulation of WNK-kinase 4 which regulates NCC, the ENaC, and the renal outer medullary potassium channel (ROMK) (32). Phenotype is varied and can present in adulthood with a mineralocorticoid resistant hyperkalaemia with hypertension and metabolic acidosis (33).

Chloride in pregnancy and paediatrics

Pregnancy is associated with haemodilution; chloride concentration is however only marginally different with perhaps a 1–5 mmol/L reduction at the lower end and potential increase at the upper end of the reference interval (34,35). Hyperchloraemic acidosis can be a feature of preeclampsia and pregnancy induced hypertension (36).

Chloride remains remarkably static in paediatric age groups with ranges not differing significantly from adults even in neonates (37). More chloride is required during pregnancy and lactation, but most people's dietary intake is perfectly adequate to accommodate this (4).

Conclusions

Investigation of chloride can be challenging, but a good understanding of sodium and acid base status will help to diagnose patients. The presented algorithms will support diagnosis by providing a step-by-step process for the clinician but cannot replace clinical experience, local or national guidelines.

Acknowledgments

Footnote

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References

1. Thongprayoon C, Cheungpasitporn W, Petnak T, et al. Hospital-Acquired Serum Chloride Derangements and Associated In-Hospital Mortality. Medicines (Basel) 2020;7:38.
2. Bandak G, Kashani KB. Chloride in intensive care units: a key electrolyte. F1000Res 2017;6:1930.
3. Marshall W, Lapsley M, Day A, et al. Clinical chemistry. 9th edition. Elsevier Inc., 2020:25-53.
4. Strohm D, Bechthold A, Ellinger S, et al. Revised Reference Values for the Intake of Sodium and Chloride. Ann Nutr Metab 2018;72:12-7.
5. Berend K, van Hulsteijn LH, Gans RO. Chloride: the queen of electrolytes? Eur J Intern Med 2012;23:203-11.
6. Kiela PR, Ghishan FK. Physiology of Intestinal Absorption and Secretion. Best Pract Res Clin Gastroenterol 2016;30:145-59.
7. McCallum L, Lip S, Padmanabhan S. The hidden hand of chloride in hypertension. Pflugers Arch 2015;467:595-603.
8. Nagami GT. Hyperchloremia - Why and how. Nefrologia

2016;36:347-53.

9. Dimeski G, Mollee P, Carter A. Effects of hyperlipidemia on plasma sodium, potassium, and chloride measurements by an indirect ion-selective electrode measuring system. Clin Chem 2006;52:155-6.

10. Morrison G. Chapter 197: Serum Chloride. In: Walker HK, Hall WD, Hurst JW. editors. Clinical Methods: The History, Physical, and Laboratory Examinations. 3rd edition. Boston: Butterworths, 1990.

11. KDIGO Clinical Practice Guideline for Acute Kidney Injury. 2012;2(Supp 1). accessed 22.1.22. Available online: https://kdigo.org/wp-content/uploads/2016/10/KDIGO-2012-AKI-Guideline-English.pdf

12. KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. 2013;3(1). accessed 22.1.22. Available online: https://kdigo.org/wp-content/uploads/2017/02/KDIGO_2012_CKD_GL.pdf

13. Rossi R, Danzebrink S, Linnenbürger K, et al. Assessment of tubular reabsorption of sodium, glucose, phosphate and amino acids based on spot urine samples. Acta Paediatr 1994;83:1282-6.

14. Emmett M. Metabolic Alkalosis: A Brief Pathophysiologic Review. Clin J Am Soc Nephrol 2020;15:1848-56.

15. Kamel KS, Halperin ML. Use of Urine Electrolytes and Urine Osmolality in the Clinical Diagnosis of Fluid, Electrolytes, and Acid-Base Disorders. Kidney Int Rep 2021;6:1211-24.

16. Brinkman JE, Sharma S. Physiology, Metabolic Alkalosis. [Updated 2021 Jul 22]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021 Jan-. Available online: https://www.ncbi.nlm.nih.gov/books/NBK482291/

17. Al Shibli A, Narchi H. Bartter and Gitelman syndromes: Spectrum of clinical manifestations caused by different mutations. World J Methodol 2015;5:55-61.

18. Wedenoja S, Höglund P, Holmberg C. Review article: the clinical management of congenital chloride diarrhoea. Aliment Pharmacol Ther 2010;31:477-85.

19. Bareil C, Bergougnoux A. CFTR gene variants, epidemiology and molecular pathology. Arch Pediatr 2020;27 Suppl 1:eS8-eS12.

20. Ozçelik U, Göçmen A, Kiper N, et al. Sodium chloride deficiency in cystic fibrosis patients. Eur J Pediatr 1994;153:829-31.

21. Bertulli C, Hureaux M, De Mutiis C, et al. A Rare Cause of Chronic Hypokalemia with Metabolic Alkalosis: Case Report and Differential Diagnosis. Children (Basel) 2020;7:212.

22. Thakker RV. Pathogenesis of Dent's disease and related syndromes of X-linked nephrolithiasis. Kidney Int 2000;57:787-93.

23. Li F, Yue Z, Xu T, et al. Dent Disease in Chinese Children and Findings from Heterozygous Mothers: Phenotypic Heterogeneity, Fetal Growth, and 10 Novel Mutations. J Pediatr 2016;174:204-210.e1.

24. Alper SL, Sharma AK. The SLC26 gene family of anion transporters and channels. Mol Aspects Med 2013;34:494-515.

25. Enslow BT, Stockand JD, Berman JM. Liddle's syndrome mechanisms, diagnosis and management. Integr Blood Press Control 2019;12:13-22.

26. Mao W, Wu J, Zhang H, et al. Increase in serum chloride and chloride exposure are associated with acute kidney injury in moderately severe and severe acute pancreatitis patients. Pancreatology 2019;19:136-42.

27. Perkins CJ, Wahl GE, Gillett MJ. A case of pseudohyperchloraemia caused by sodium nitrate ingestion. Clin Toxicol (Phila) 2022;60:259-61.

28. Jacob J, Lavonas EJ. Falsely normal anion gap in severe salicylate poisoning caused by laboratory interference. Ann Emerg Med 2011;58:280-1.

29. Wang T, Diamandis EP, Lane A, et al. Variable selectivity of the Hitachi chemistry analyzer chloride ion-selective electrode toward interfering ions. Clin Biochem 1994;27:37-14.

30. Routh JI, Paul WD. Assessment of interference by aspirin with some assays commonly done in the clinical laboratory. Clin Chem 1976;22:837-42.

31. Wang YT, Yang SY, Wu VC, et al. Pseudohyperchloraemia due to bromvalerylurea abuse. Nephrol Dial Transplant 2005;20:1767-8.

32. Mabillard H, Sayer JA. The Molecular Genetics of Gordon Syndrome. Genes (Basel) 2019;10:986.

33. OMIM Entry - % 145260 - PSEUDOHYPOALDOSTERONISM, TYPE IIA; PHA2A. Available online: https://www.omim.org/entry/145260?search=pseudohypoaldosteronism%20type%20II&highlight=ii%20pseudohypoaldosteronism%20type (Accessed 27.04.2022)

34. Larsson A, Palm M, Hansson LO, et al. Reference values for clinical chemistry tests during normal pregnancy. BJOG 2008;115:874-81.

35. Abbassi-Ghanavati M, Greer LG, Cunningham FG. Pregnancy and laboratory studies: a reference table for clinicians. Obstet Gynecol 2009;114:1326-31.

36. Ortner CM, Combrinck B, Allie S, et al. Strong ion and weak acid analysis in severe preeclampsia: potential clinical significance. Br J Anaesth 2015;115:275-84.
37. Tahmasebi H, Higgins V, Woroch A, et al. Pediatric reference intervals for clinical chemistry assays on Siemens ADVIA XPT/1800 and Dimension EXL in the CALIPER cohort of healthy children and adolescents. Clin Chim Acta 2019;490:88-97.