Investigative algorithms for disorders affecting alkalosis: 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. By the end of the article, the reader will be able to interpret arterial blood gases, and order and interpret appropriate investigations when faced with an alkalotic patient.

Methods: A narrative, focused literature review was performed using PubMed, OMIM and Google during September 2021 to January 2022 to identify references published from database inception to January 2022; reference lists from these articles were also used. Language was restricted to English.

Key Content and Findings: Acid balance in the body is tightly controlled with the respiratory and renal systems, and acute and chronic compensatory mechanisms exist to help maintain this homeostasis. The laboratory approach to diagnosis of alkalosis, respiratory and metabolic, is presented. It should be noted that symptoms caused by changes in pH are not well established as they rarely occur in isolation e.g., are associated with changes in partial pressure of carbon dioxide (pCO_2).

Conclusions: Diagnostic schema will be presented and the limitations of the laboratory tests discussed. The algorithm, by focusing on the approach to the investigation of alkalosis, should support healthcare professionals to efficiently and rapidly diagnose most causes of the alkalotic state.

Keywords: Alkalosis; investigation; algorithm; metabolic alkalosis; respiratory compensation

Introduction

The acid base balance in the blood is tightly controlled using the respiratory and renal systems. Acute and chronic compensatory mechanisms facilitate homeostasis, where the respiratory system is used in acute alkalosis, and the renal system is used in chronic alkalosis. Due to the complex interplay of various systems, including compensatory mechanisms, multi-system diseases or concomitant medications, the cause of an alkalotic state may not be immediately apparent (1). As the members of the healthcare team expand, laboratory diagnostic tests are ordered more frequently by people with less experience in either test selection or diagnosis of metabolic disease. Performing the incorrect test can create spuriously abnormal results leading to patient anxiety and further inappropriate tests. This can delay the correct diagnosis, making the process clinically and economically inefficient. Choosing the correct test first time can greatly improve the experience for the patient as
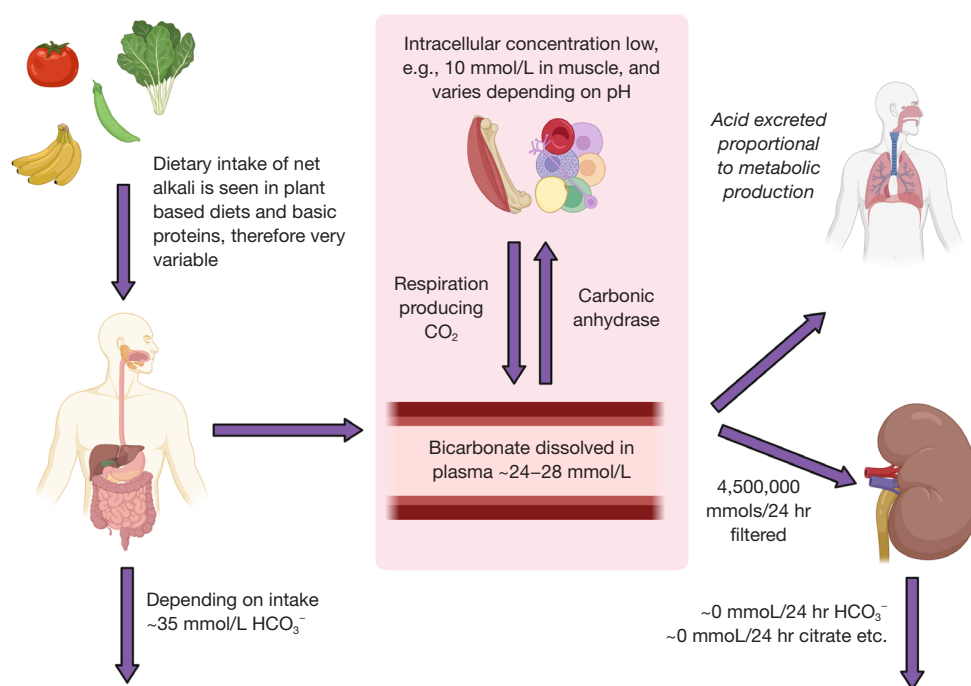
Figure 1 A basic overview of the distribution and homeostasis of bicarbonate in humans. Ingestion is normally matched by excretion. Dietary intake varies widely and 100% of bicarbonate is reabsorbed renally in normal circumstances. Serum concentration adapts to maintain normal pH.

well as the quality and efficiency of healthcare. Therefore the following article will focus on the laboratory tests to aid diagnosis of alkalosis, both respiratory and metabolic, to identify the cause of the imbalance. It should be noted that symptoms caused by changes in pH are not well established as they rarely occur in isolation, e.g., are associated with changes in partial pressure of carbon dioxide (pCO_2). This article is not meant to replace the many excellent guidelines and reviews on pathophysiology and treatment. We present the following article in accordance with the Narrative Review reporting checklist (available at https://jlpm. amegroups.com/article/view/10.21037/jlpm-22-8/rc).

Methods

The narrative literature review was created by searching Medline, Google Scholar, OMIM and seminal texts. The diagnostic algorithms were then created using the information gathered for the literature review. 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 S1).

Biological mechanism of alkalosis

The metabolic conversion of carbon dioxide to hydrogen and bicarbonate ions, metabolised by carbonic anhydrase, is the basic chemical step responsible for the acid-base state of the circulating plasma (see below) (2).

$$H + HCO_3 = H_2CO_3 \qquad [1]$$
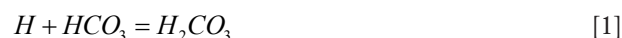
Alkali in diet varies widely; however, diets with a lower meat content (vegetarian or vegan) are more likely to be alkaline. Bicarbonate is reabsorbed by the kidneys and carbon dioxide excretion is regulated to expel excess acid production (*Figures 1,2*) (3).

Compensation

The pCO_2 is imperative to determine the cause of an acid-base imbalance (*Figure 3*) and, depending on how acute the problem is, you may see signs of compensation developing (1). Acute compensation involves retaining acid in the form of carbon dioxide by reducing ventilation. The kidneys normally reabsorb 100% of all bicarbonate (*Figures 1,2*) (4). In chronic alkalosis, the kidneys reduce bicarbonate
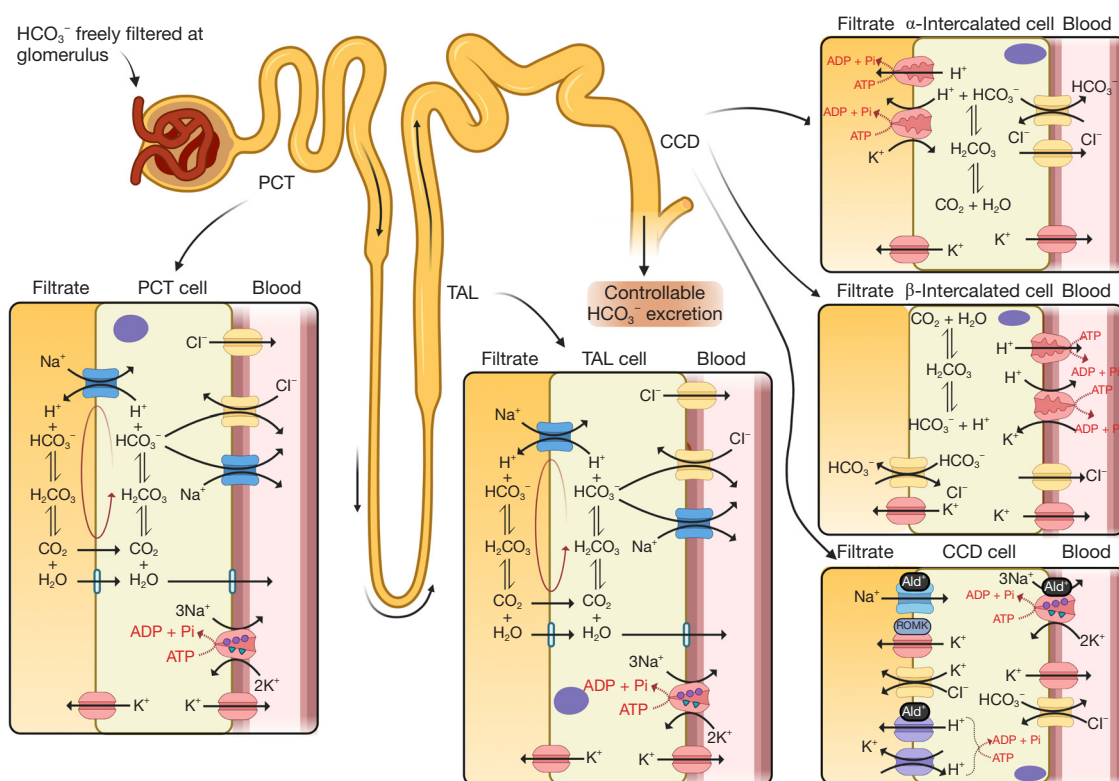
Figure 2 Simplified diagram of the major proteins involved in renal bicarbonate handling in humans. PCT, proximal convoluted tubule; ADP, adenosine disphosphate; ATP, adenosine triphosphate; Pi, inorganic phosphate; TAL, thick ascending limb; CCD, cortical collecting duct; Ald, aldosterone; ROMK, renal outer medullary potassium channel.

reabsorption, and this becomes more pronounced as the state progresses in severity. These changes in pCO_2 and bicarbonate concentration can be estimated (particularly if the time of onset and type of alkalosis is known) (*Table 1*) (1). It is important to note that over-compensation does not occur and the compensation formulae were originally established in canine models (5). Most of these have been replaced by formulae derived from small human studies but although linear, there is scatter, and therefore these formulae are estimates and are affected by time of onset, presence of mixed disorders and treatments.

Consequences of alkalosis

Hyperchloraemic hypokalaemia

Alkalosis largely affects potassium, causing prominent hypokalaemia (*Table 1*) (4). This is due to H^+ exchange with intracellular K^+, and increased K^+ excretion via renal sodium pump and apical tubular potassium permeability

activation (in an attempt to retain H^+). Renal compensation, i.e., bicarbonate excretion, requires anion exchange in the kidneys and tissues in order to maintain electrical neutrality. Bicarbonate is exchanged with chloride ions, which is why alkalosis is associated with hyperchloraemic hypokalaemia (4).

Hypophosphataemia

Hypophosphataemia is seen in alkalosis, as the change in cellular pH stimulates phosphofructokinase, which increases glycolysis and ATP production (6). Extracellular phosphate therefore shifts intracellularly to satisfy the demand.

Hypocalcaemia and hypomagnesaemia

Other laboratory parameters affected by alkalosis include a decrease in ionised (not total) serum calcium, as the positive binding sites on proteins, mainly albumin, are no longer occupied with protons (7). The same process affects magnesium although to a lesser degree, as a lower

A

Alkalosis (See Box 1)
↓
Assess partial pressure of CO_2
↓

Normal/high $PaCO_2$
→ Metabolic alkalosis
→ Compensation as expected? (See Box 2)
→ Yes / No. mixed disorder? (See Box 3)
→ Measure 24 hour Urine Cl^- (See Box 4)
→ Urine Cl ≤10 mmol/L / Urine Cl >20 mmol/L
→ Chloride responsive alkalosis (See Box 5)
→ Review medication (See Box 6) — Not applicable
→ Measure blood pressure
→ Normal / High
→ HypoK⁺, hyperCa²⁺ or blood products? (See Box 7) / Mineralocorticoid excess (See Box 8)

Low $PaCO_2$
→ Respiratory alkalosis
→ Compensation as expected? (See Box 2)
→ Yes / No. mixed disorder? (See Box 3)
→ Review medication (See Box 9) — Not applicable
→ Assess partial pressure of O_2
→ Normal / Low
→ CNS stimulation? (See Box 10) — Not applicable / Hypoxia (See Box 12)
→ Other causes (See Box 11)

B

Box 1-Alkalosis
Raised pH, preferably measured on an arterial blood gas

Box 2-Expected compensation
See Table 1 in the text. This is an estimate only and will depend on duration of acidosis and treatments among other factors

Box 3-Mixed disorder
There may be simultaneous alkalosis with acidosis e.g., sepsis with respiratory failure and dehydration (respiratory acidosis with metabolic alkalosis), or salicylate toxicity (metabolic acidosis with respiratory alkalosis).
Note respiratory alkalosis can occur after resolution of a metabolic acidosis as the hyperventilation can persist up to 48 hours

Box 4-Urinary chloride
A 24 hr collection is preferred off all diuretics. Excretion is related to Cl^- load, K^+ channel expression and acid base status, which is why conditions such as hyperaldosteronism can be associated with high or low Cl^- depending on whether there is salt reabsorption or the alkalsois drives Cl^- loss predominantly

Box 5-Cl^- responsive alklosis
• Vomiting, congenital chloride losing diarrhoea, cystic fibrosis; contraction alkalosis
• Drugs e.g., diuretic, alkalotic agents, strong acid salts (lactate, citrate), poorly reaborbable anions e.g., penicillin, calcium- or milk-alkali syndrome
• Hyponatraemia or hypokalaemia
• Anorexia nervosa

Box 6-Medications
• Mineralocorticoids e.g., liquorice, carbenoxolone
• Diuretics

Box 7-Hypokalaemia or citrate
Hypokalaemia e.g., hypomagnesaemia, Bartter; refeeding syndrome; hypercalcaemia (not PTH related); transfusion of citrated products

Box 8-Mineralocorticoid excess
• Primary hyperaldosteronism, Cushing, renal artery stenosis
• Liddle,11- and 17-alphahydroxylase deficiencies

Box 9-Medications
Respiratory stimulants e.g., salicylates, xanthines, sympathomimetics, nicotine, doxapram, progesterone, thyroxine, nikethimide

Box 10-CNS stimulation
Fever, head injury, brain tumour, encephalitis, cerebrovascular disease, voluntary hyperventilation, anxiety states, irritating lesions of airways

Box 11-Othe causes (non cerebral)
• Pregnancy
• Mechanical hyperventilation
• Heat exposure
• Recovery from metabolic acidosis
• Liver failure
• Hyponatraemia, severe
• Gram negative septicaemia

Box 12-Hypoxia
• High altitude,
• Pulmonary ventilation/perfusion imbalance, pulmonary shunts
• Hypotension
• Early and non-severe pulmonary diffusion problems such as asthma, pneumonia and heart failure

Figure 3 Diagnostic laboratory algorithm for alkalosis in humans with supportive information. (A) Diagnostic laboratory algorithm for alkalosis in humans; (B) boxes providing supportive information for diagnostic algorithm Figure 3A. $PaCO_2$, arterial partial pressure of carbon dioxide; CNS, central nervous system.

Table 1 The relationship of bicarbonate concentration and partial pressure of arterial carbon dioxide and the effect of pH level on plasma potassium concentration in alkalosis

Type of alkalosis	Change
Fall in [HCO_3^-] per decrease in $PaCO_2$	
Acute respiratory alkalosis	0.2 mmol/L per mmHg (0.133 kPa)
Chronic respiratory alkalosis	0.4 mmol/L per mmHg (0.133 kPa)
Rise in $PaCO_2$ per increase in [HCO_3^-]	
Metabolic alkalosis	0.7 mmHg (0.09 kPa) per mmol/L
[K^+]p change for every 0.1 elevation in pH	
Respiratory alkalosis	0.3 mmol/L reduction
Metabolic alkalosis	0.2 mmol/L reduction

Acute meaning within hours and chronic several days. $PaCO_2$, arterial partial pressure of carbon dioxide; p, plasma.

concentration of magnesium binds albumin (30% for magnesium, rather than 50% for ionised calcium) (8). The person may manifest symptoms of hypocalcaemia and hypomagnesaemia due to low ionised concentrations. However, there may be no measurable abnormality as the total serum concentrations may not change, and ionised calcium is adjusted for pH in most blood gas reports.

Hyperlactataemia

Hyperlactataemia can be caused by alkalosis, primarily due to the stimulation of glycolysis. The increased pyruvate production drives lactate production, and the alkalosis stimulates bicarbonate loss in the kidneys, which in turn prevents renal lactate excretion (to maintain electroneutrality as lactate is negatively charged) (7). Alkalosis also causes a shift in the oxygen dissociation curve,

reducing oxygen delivery to tissues and increasing anaerobic respiration (and lactate concentration). The reduction in oxygen delivery causes hyperventilation (which blows off more carbon dioxide exacerbating alkalosis), and the alkalosis also impairs mitochondrial respiration (producing more lactate) (9). Lactate also causes vasoconstriction, exacerbating tissue hypoxia and hyperlactataemia (10). This all can complicate the picture and make diagnosis difficult in some rare cases.

Pre-analytical factors: patients, specimens and laboratory tests

Patient preparation

Pre-analytical issues must be considered when assessing acid-base disorders, and although rarer, analytical issues can also occur. The patient must be breathing at their basal rate when the sample is taken, and they should be prone and as relaxed as possible (10,11).

Specimen tubes and collection vessels

Specimen tubes should be glass, but are mostly plastic, which is more practical, but slightly permeable to oxygen. All air should be expelled from syringes first and only heparin should be used as an anticoagulant, as citrate, EDTA and fluoride alter blood pH (12). Underfilling specimen tubes, which contain liquid anticoagulant, can lead to dilution artefact (reducing pCO_2 and bicarbonate concentration), therefore liquid containing tubes should be filled to their maximum (12). Heparin can be acidic, therefore manufacturing variation may result in spurious acidosis (13). Specimens should be analysed immediately, if possible, to prevent metabolism *in vitro* affecting results (12).

Specimen type

If venous blood is measured instead of arterial, there will be differences in the respiratory gases (high pCO_2) (14). The issue is that the expected differences may apply to well, stable, patients; and the differences may be considerably more marked in severely ill patients (4). However, adjustment formulae have been validated in an attempt to limit arterial venesection, which is not without risk, and performance may be acceptable as long as the limitations are understood (15). Capillary sampling is also not recommended, as is affected by changes to the peripheral

circulation (12). However, using sites such as the ear lobe that have been 'arterialised' (warmed and rubbed to create hyperaemia) first can improve the utility. This is not an appropriate method for pO_2, and both pH and pCO_2 can be affected by sampling technique (12). In the following paper, we will refer to measurements performed on arterial samples for blood gases (or serum for other analytes).

Patient temperature

Blood gas analysers measure pH, pCO_2, and pO_2; and then calculate the rest of the derivate parameters. These values are then also adjusted for patient temperature. This practice, albeit controversial, will affect results, depending on whether users correctly enter temperature upon analysis (12). It is true, however, that the 'reference intervals' apply; irrespective of the temperature of the patient. The alveolar-arterial gradient must use temperature adjusted values to avoid spurious results (16).
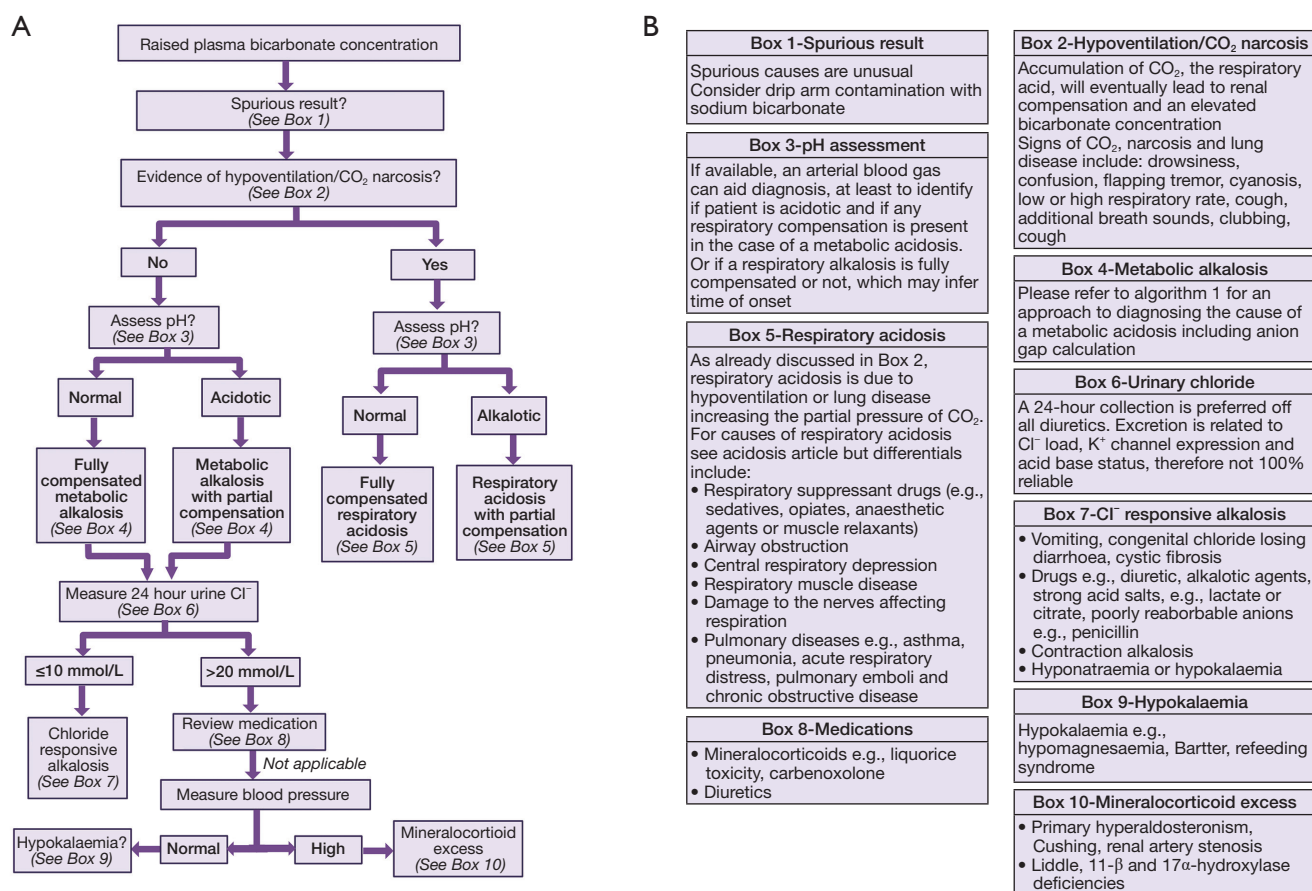
Diagnostic algorithms

An algorithm providing suggestions on an approach to the diagnosis of alkalosis is provided (*Figure 3*), followed by a high bicarbonate in isolation, for example, in cases where you do not have an arterial blood gas analysis (*Figure 4* and see article in same series on acidosis). If the acid-base status is not known, then a high bicarbonate is effectively either a metabolic alkalosis, or compensation for respiratory acidosis. Finally an algorithm specifically looking at hypokalaemic metabolic alkalosis is provided (*Figure 5*). Importantly, the tests for an acid-base disorder are never completely diagnostic, and the conclusion must be weighed by the clinical evidence (2). Pre-existing acid base disorders, mixed disorders, renal impairment, fluid status, and other therapies, will all affect the results; so correlate closely with the clinical situation (2).

Cautions with urine testing

Urinary measurement is recommended, provided that renal function is normal, and the patient is off all diuretics for as long as possible, e.g., 2 weeks (17). Note for chloride that concentrations between 10 and 20 mmol/L are missing (18). There is variation in the literature such as a single threshold of 20 or 15 mmol/L (19). However, due to the multiple factors affecting urinary excretion, intermediate results may not be diagnostic.

A

B

Box 1-Spurious result
Spurious causes are unusual. Consider drip arm contamination with sodium bicarbonate

Box 3-pH assessment
If available, an arterial blood gas can aid diagnosis, at least to identify if patient is acidotic and if any respiratory compensation is present in the case of a metabolic acidosis. Or if a respiratory alkalosis is fully compensated or not, which may infer time of onset

Box 5-Respiratory acidosis
As already discussed in Box 2, respiratory acidosis is due to hypoventilation or lung disease increasing the partial pressure of CO_2. For causes of respiratory acidosis see acidosis article but differentials include: • Respiratory suppressant drugs (e.g., sedatives, opiates, anaesthetic agents or muscle relaxants) • Airway obstruction • Central respiratory depression • Respiratory muscle disease • Damage to the nerves affecting respiration • Pulmonary diseases e.g., asthma, pneumonia, acute respiratory distress, pulmonary emboli and chronic obstructive disease

Box 8-Medications
• Mineralocorticoids e.g., liquorice toxicity, carbenoxolone • Diuretics

Box 2-Hypoventilation/CO_2 narcosis
Accumulation of CO_2, the respiratory acid, will eventually lead to renal compensation and an elevated bicarbonate concentration. Signs of CO_2, narcosis and lung disease include: drowsiness, confusion, flapping tremor, cyanosis, low or high respiratory rate, cough, additional breath sounds, clubbing, cough

Box 4-Metabolic alkalosis
Please refer to algorithm 1 for an approach to diagnosing the cause of a metabolic acidosis including anion gap calculation

Box 6-Urinary chloride
A 24-hour collection is preferred off all diuretics. Excretion is related to Cl^- load, K^+ channel expression and acid base status, therefore not 100% reliable

Box 7-Cl^- responsive alkalosis
• Vomiting, congenital chloride losing diarrhoea, cystic fibrosis • Drugs e.g., diuretic, alkalotic agents, strong acid salts, e.g., lactate or citrate, poorly reaborbable anions e.g., penicillin • Contraction alkalosis • Hyponatraemia or hypokalaemia

Box 9-Hypokalaemia
Hypokalaemia e.g., hypomagnesaemia, Bartter, refeeding syndrome

Box 10-Mineralocorticoid excess
• Primary hyperaldosteronism, Cushing, renal artery stenosis • Liddle, 11-β and 17α-hydroxylase deficiencies

Figure 4 Diagnostic laboratory algorithm for raised bicarbonate concentration in humans with supportive information. (A) Diagnostic laboratory algorithm for raised bicarbonate concentration in humans; (B) boxes providing supportive information for diagnostic algorithm *Figure 4A*.

Fractional excretion of sodium is not recommended for distinguishing the cause of hypokalaemic metabolic alkalosis; demonstrating another limitation of this type of measurement (20). Basically, at a steady state, you cannot excrete significantly more or less electrolyte than you intake, therefore, eventually, irrespective of the underlying pathophysiology, the body adapts to keep the 'high', or 'low', electrolyte state steady (20).
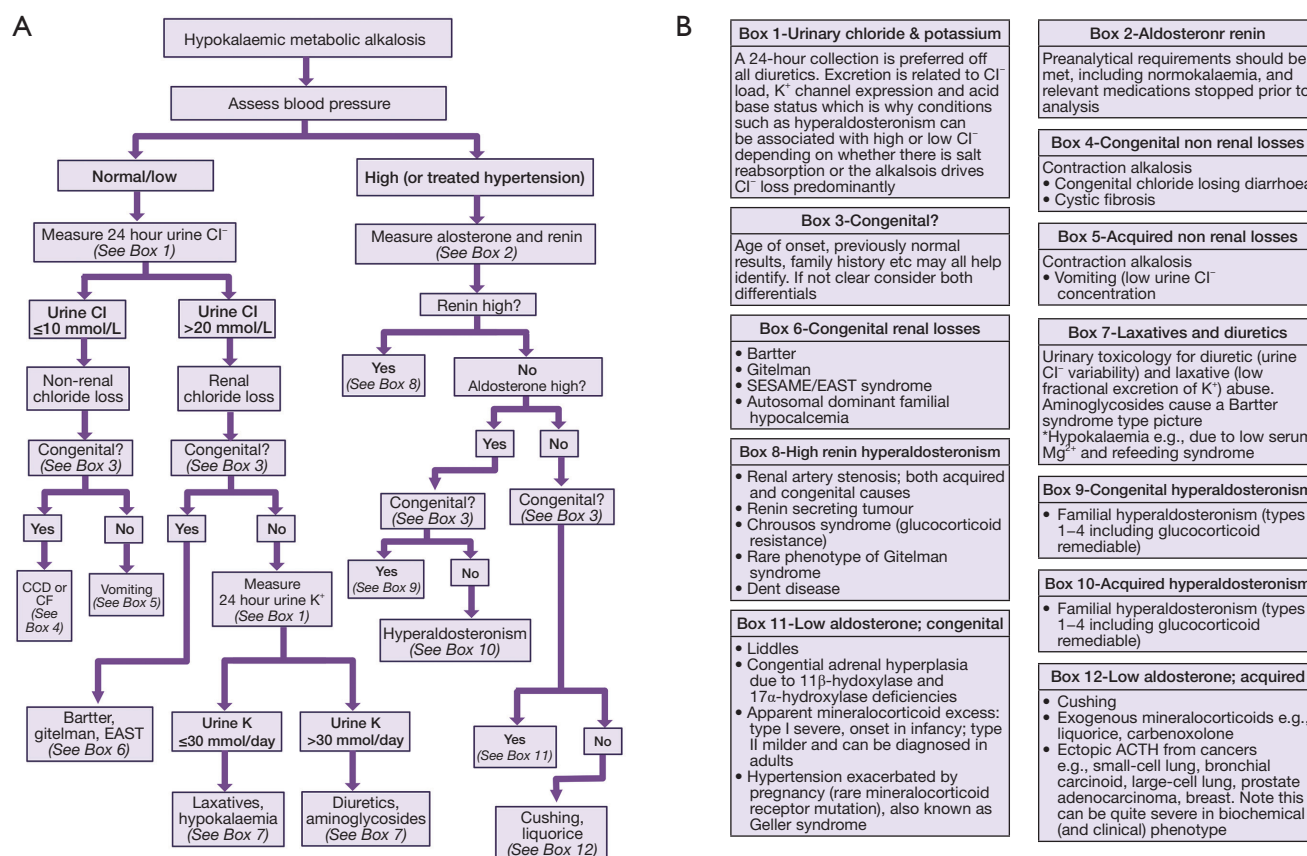
Cautions with aldosterone and renin sampling

Aldosterone and renin are important tests in the algorithms. Effectively, fluid status and salt intake should be adequate, and potassium should be normal before sampling for these tests. If salt intake is increased prior to the test, it can worsen the hypokalaemia. Antihypertensive drugs and patient posture will also affect the results and chilling the

sample for renin is problematic (for example, user wrongly transported the sample on ice) (21). Consider stopping diuretics four weeks prior to the test, and β-adrenergic blockers, α-2 agonists (e.g., clonidine, α-methyldopa), non-steroidal anti-inflammatory drugs, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, renin inhibitors, and dihydropyridine calcium channel antagonists, perhaps more controversially, 2 weeks before the test (7). It is worth noting that the ratio can be less affected by preanalytical factors, such as drugs, than the isolated measurements.

Alkalosis

Respiratory alkalosis

Respiratory alkalosis is caused by hyperventilation, which

A

Hypokalaemic metabolic alkalosis
↓
Assess blood pressure

Normal/low | High (or treated hypertension)

Normal/low
Measure 24 hour urine Cl^- *(See Box 1)*

Urine Cl ≤10 mmol/L → Non-renal chloride loss → Congenital? *(See Box 3)* → Yes: CCD or CF *(See Box 4)* / No: Vomiting *(See Box 5)*

Urine Cl >20 mmol/L → Renal chloride loss → Congenital? *(See Box 3)* → Yes: Bartter, gitelman, EAST *(See Box 6)* / No: Measure 24 hour urine K^+ *(See Box 1)*

Urine K ≤30 mmol/day → Laxatives, hypokalaemia *(See Box 7)*
Urine K >30 mmol/day → Diuretics, aminoglycosides *(See Box 7)*

High (or treated hypertension)
Measure aldosterone and renin *(See Box 2)* → Renin high?
Yes *(See Box 8)*
No → Aldosterone high?
Yes → Congenital? *(See Box 3)* → Yes *(See Box 9)* / No → Hyperaldosteronism *(See Box 10)*
No → Congenital? *(See Box 3)* → Yes *(See Box 11)* / No → Cushing, liquorice *(See Box 12)*

B

Box 1-Urinary chloride & potassium
A 24-hour collection is preferred off all diuretics. Excretion is related to Cl^- load, K^+ channel expression and acid base status which is why conditions such as hyperaldosteronism can be associated with high or low Cl^- depending on whether there is salt reabsorption or the alkalsois drives Cl^- loss predominantly

Box 3-Congenital?
Age of onset, previously normal results, family history etc may all help identify. If not clear consider both differentials

Box 6-Congenital renal losses
• Bartter
• Gitelman
• SESAME/EAST syndrome
• Autosomal dominant familial hypocalcemia

Box 8-High renin hyperaldosteronism
• Renal artery stenosis; both acquired and congenital causes
• Renin secreting tumour
• Chrousos syndrome (glucocorticoid resistance)
• Rare phenotype of Gitelman syndrome
• Dent disease

Box 11-Low aldosterone; congenital
• Liddles
• Congenital adrenal hyperplasia due to 11β-hydroxylase and 17α-hydroxylase deficiencies
• Apparent mineralocorticoid excess: type I severe, onset in infancy; type II milder and can be diagnosed in adults
• Hypertension exacerbated by pregnancy (rare mineralocorticoid receptor mutation), also known as Geller syndrome

Box 2-Aldosteronr renin
Preanalytical requirements should be met, including normokalaemia, and relevant medications stopped prior to analysis

Box 4-Congenital non renal losses
Contraction alkalosis
• Congenital chloride losing diarrhoea
• Cystic fibrosis

Box 5-Acquired non renal losses
Contraction alkalosis
• Vomiting (low urine Cl^- concentration)

Box 7-Laxatives and diuretics
Urinary toxicology for diuretic (urine Cl^- variability) and laxative (low fractional excretion of K^+) abuse. Aminoglycosides cause a Bartter syndrome type picture
*Hypokalaemia e.g., due to low serum Mg^{2+} and refeeding syndrome

Box 9-Congenital hyperaldosteronism
• Familial hyperaldosteronism (types 1–4 including glucocorticoid remediable)

Box 10-Acquired hyperaldosteronism
• Familial hyperaldosteronism (types 1–4 including glucocorticoid remediable)

Box 12-Low aldosterone; acquired
• Cushing
• Exogenous mineralocorticoids e.g., liquorice, carbenoxolone
• Ectopic ACTH from cancers e.g., small-cell lung, bronchial carcinoid, large-cell lung, prostate adenocarcinoma, breast. Note this can be quite severe in biochemical (and clinical) phenotype

Figure 5 Diagnostic laboratory algorithm for hypokalaemic metabolic alkalosis in humans with supportive information. (A) Diagnostic laboratory algorithm for hypokalaemic metabolic alkalosis in humans; (B) boxes providing supportive information for diagnostic algorithm *Figure 5A*. *Note hypokalemia can also be the cause metabolic alkalosis. CCD, congenital chloride diarrhoea; CF, cystic fibrosis; SESAME, seizures, sensorineural deafness, ataxia, mental retardation and electrolyte imbalance syndrome; EAST, epilepsy, ataxia, sensorineural deafness and tubulopathy syndrome; ACTH, adrenocorticotrophic hormone.

blows off carbon dioxide (a respiratory acid), hence patients are diagnosed with respiratory alkalosis if they present with an elevated blood pH and low pCO_2 (7). Bicarbonate should be low however the reduction is dependent of the time of onset and bicarbonate may be normal in acute respiratory alkalosis (1). Common causes of pure respiratory alkalosis include anxiety attacks, in which the patient hyperventilates, and asthma attacks, where the patient hyperventilates to maintain pO_2 but consequently blows off carbon dioxide (7). A normal pCO_2 identified during an asthma attack is a poor prognostic indicator demonstrating respiratory fatigue (22).

Metabolic alkalosis

Metabolic alkalosis is typically caused by either an increase in other alkaline agents or renal/gut loss of protons. Arterial

blood gasses show elevated pH, bicarbonate and pCO_2 (1). Other laboratory findings include: decreased serum ionised calcium, hypokalaemia and hypophosphataemia (see above).

Chloride concentration can be useful due to the effect of aldosterone (see article in series on chloride).

Metabolic alkalosis: saline responsive

Aldosterone is secreted primarily in response to hypovolaemia, and stimulates salt (NaCl) and water reabsorption in the kidney. To maintain electroneutrality, sodium is exchanged for potassium and hydrogen ions. This results in an alkalosis that should respond to saline treatment (called 'saline responsive' alkalosis) and is indicated by a spot urine chloride concentration ≤10 mmol/L (or 20 mmol/L, see above) (12). Causes include: losses from the gut (vomiting, suction, diarrhoea), or skin [cystic fibrosis (CF)], and drugs

(exogenous alkali, previous diuretic therapy) (18). Chloride responsive alkalosis can also be seen in anorexia nervosa and calcium-alkali (milk-alkali) syndrome (23).

Metabolic alkalosis: calcium-alkali syndrome

Calcium-alkali syndrome is defined by (hypokalaemic) metabolic alkalosis, hypercalcaemia, and renal failure; it occurs following ingestion of compounds such as calcium salts, dairy products, magnesium oxide and sodium bicarbonate for osteoporosis or gastric ulcer treatment (24). Note that hypercalcaemia from malignant causes can cause a saline unresponsive metabolic alkalosis due to release of buffers (e.g., phosphate) from bone (25).

Other causes of metabolic alkalosis

Other causes of volume and/or electrolyte losses (and secondary hyperaldosteronism) include drug abuse or surreptitious vomiting. Laxative abuse can be identified by direct measurement of drugs and metabolites in urine, however a low fractional excretion of potassium can be suggestive (26). Furthermore, urine toxicology can detect diuretic abuse, although urine chloride variability is suggestive (27). Use of thiazide diuretics resembles Gitelman syndrome, with hypochloraemia, hypokalaemia and hypomagnesaemia, with inappropriately high urine chloride if taking medication (see below and *Figure 5*) (27). Loop diuretics will also cause a hypochloremic, hypokalaemic metabolic alkalosis, but may also demonstrate hyperuricaemia and hypercalciuria (like Bartter syndrome) (28). In suspected bulimia/surreptitious vomiting, low urine chloride concentration can be suggestive (29).

Metabolic alkalosis: saline unresponsive

If urine chloride is ≥20 mmol/L, this suggests it will be saline unresponsive or there is massive renal chloride loss in diuresis (18). Refeeding syndrome causes a saline unresponsive metabolic alkalosis by raising bicarbonate levels and possibly proton movement to the intracellular compartment (30). Blood transfusion containing citrate is also a cause, due to citrate being metabolised to bicarbonate (31).

Primary hyperaldosteronism is indicated by the combination of hypertension, low serum renin, and raised plasma aldosterone:renin activity ratio (32). There are a number of rare causes of metabolic alkalosis, which can mimic hyperaldosteronism among others (32). Blood pressure and aldosterone concentration can aid diagnosis (32).

Mixed disorders of alkalosis

The presence of mixed disorders can complicate diagnosis. One example is salicylate toxicity, as it is a respiratory stimulant, but salicylate in higher concentrations can also cause vomiting and hence a metabolic alkalosis (33). Additionally, salicylate is an acid itself. Use of diuretics (metabolic alkalosis) with chronic lung disease (respiratory acidosis), and vomiting (metabolic alkalosis) with renal failure (metabolic acidosis), are some other examples of mixed disorders (34). The combination of respiratory and metabolic alkalosis can also exacerbate, and complicate, the diagnosis; this is seen in hyperventilated patients with gastric losses.

Pregnancy and paediatric values

Pregnancy

Pregnancy leads to haemodilution, changes in the respiratory system, and reduction in bicarbonate concentration by 2–6 mmol/L (25%), effectively causing a fully compensated respiratory alkalosis (35,36). However, it is important not to disregard a low bicarbonate concentration automatically during pregnancy, particularly if they are presenting with possible metabolic acidosis. Breathless pregnant women have lost some of their buffering capacity and so are more sensitive to acidosis. Blood pH may increase slightly in pregnancy; arterial blood by 0.01 at both the upper and lower end of the normal range, and slightly higher in venous blood (9).

Rare pregnancy causes of alkalosis

It is worth noting that there is a very rare mutation in *NR3C2* gene for the mineralocorticoid receptor, which makes it sensitive to other steroids such as progesterone. A syndrome like Liddle syndrome, called 'hypertension exacerbated by pregnancy' or Geller syndrome, is observed in these patients (low renin activity, low aldosterone, hypokalaemia, hypertension with metabolic alkalosis) (37). This is distinct from other causes of hypertension, like pre-eclampsia, and may present as hypokalaemia during pregnancy also (38,39).

Paediatric considerations

Children approach adult pCO_2 by 5 years of age, but neonates have a lower pCO_2 that increases over time (40). The pH and bicarbonate concentrations are assumed to be equivalent to adult normal reference intervals.

Rare conditions and complicating issues

There are some rare causes of hypokalaemic metabolic alkalosis (*Figure 5*). These conditions will be discussed below, starting with those associated with hypertension.

Rare causes associated with hypertension

Apparent mineralocorticoid excess (AME)

AME syndrome causes hypertension and a hypokalaemic metabolic alkalosis. AME patients have inactivating mutation in the *HSD11B2* gene encoding 11β-hydroxysteroid dehydrogenase type 2, which converts cortisol to a form that is inactive at the mineralocorticoid receptor, cortisone (32). This is identical to the effect of liquorice, where glycyrrhizic acid, or glycyrrhetinic acid, inhibit the same enzyme. This enzyme is also saturated in hypercortisolaemia, and hence why Cushing and the rarer cause, ectopic ACTH secreting tumours, also cause metabolic alkalosis with hypokalaemia; due to cortisol activation of the mineralocorticoid receptor (32).

There are two types of AME; type I, a more severe form, presenting in infancy with failure to thrive and prominent hypertension, and a much milder type II, which is usually diagnosed in adulthood (41). Depending on local availability of tests to confirm AME, urine steroid profiles help isolate the enzyme deficiency, as well as genetic testing (42). However, blood pressure, and renin activity and aldosterone measurements, are critical for preventing misdiagnosis of Bartter syndrome (6).

Liddle syndrome

Liddle syndrome is caused by activating mutations in the subunits genes *SCNN1A*, *SCNN1B*, *SCNN1G* of the epithelial sodium channel (ENaC) that is usually regulated by aldosterone (37). Again, Liddle syndrome is another cause of hypertension with hypokalaemic metabolic alkalosis (37). Although onset occurs in childhood, it has been picked up in adults as the condition, although autosomal dominant, has wide phenotypic variation, with some being normokalemic and normotensive (11). Phenotypically, it resembles primary hyperaldosteronism, but has low renin activity and aldosterone concentration, and urine steroids missing the characteristic abnormalities found in AME and congenital adrenal hyperplasia (CAH) (37). Genetic confirmation is needed for a final diagnosis (37).

Geller and Chrousos syndrome

Geller syndrome is another rare syndrome that mimics hyperaldosteronism and Liddle syndrome, due to an activating mutation of the mineralocorticoid receptor (see pregnancy section). In addition, mutations in the glucocorticoid receptor make it insensitive, and results in increased secretion of steroid hormones, inducing hyperaldosteronism (43). Therefore, Chrousos syndrome, or primary generalised familial, or sporadic, glucocorticoid resistance is another cause, however in this case the aldosterone concentration will be high (15).

CAH

Aldosterone synthesis defects occur in patients with CAH. However, metabolic alkalosis will not normally occur unless 11-deoxycorticosterone concentration is increased, leading to enhanced mineralocorticoid activity (33). Therefore, the enzyme deficiencies of 11β-hydroxylase and 17α-hydroxylase can cause hypertension, and hypokalaemic metabolic alkalosis, unlike the usual phenotype associated with CAH (44).

Familial hyperaldosteronism (FH)

FH is a collection of autosomal dominant genetic disorders causing an over production of aldosterone (45-47). FH Type 1 (FH-1) is known as glucocorticoid-remediable aldosteronism (GRA), an autosomal dominant condition where the genes *CYP11B1* and *CYP11B2* (aldosterone synthase) are fused, causing aldosterone secretion to become regulated by adrenocorticotrophic hormone (ACTH). Aldosterone is switched off in the presence of glucocorticoids, such as dexamethasone, which suppress ACTH. Clinically, it presents as moderate to severe hypertension that is fairly resistant to treatment, usually presenting at under 30 years of age. There is phenotypic variation in FH-1, so family history of primary aldosteronism may not be immediately obvious, but there may be a history of premature haemorrhagic stroke e.g., <40 years old (48). A dexamethasone suppression test, looking for aldosterone suppression or blood pressure improvement, can indicate the diagnosis, as well as urine steroid profiling (20). Not all cases are hypokalaemic.

FH-2 shows incomplete penetrance, however mutations in the chloride channel gene, *CLCN2*, increase chloride conductance in the zona glomerulosa, which results in autonomous aldosterone synthesis (18). FH-3 clinically is similar to primary hyperaldosteronism, with significant adrenal hyperplasia or adenoma. This is due to mutations in

the potassium channel gene *KCNJ5* and should be indicated by aldosteronism presenting in children (<10 years old), and family history of adrenal hypertension. Genetic testing is available, but otherwise the clinical features are like primary hyperaldosteronism. FH-4 is caused by mutations in *CACNA1H* gene and was identified in children under 10 years old presenting with primary hyperaldosteronism (19).

Conditions associated with normotension or hypotension

Bartter and Gitelman syndromes

There are also rare conditions causing hypokalaemic metabolic alkalosis, associated with low or normal blood pressure. Perhaps the most well-known are the tubulopathies: Bartter and Gitelman syndromes, affecting approximately 1 in 100,000 and 25 in 100,000 respectively (49). These tubulopathies are autosomal recessive conditions, causing salt wasting and hence hyperaldosteronism; mimicking the effects of loop and thiazide diuretics with hypochloraemia also. Bartter syndrome affects the thick ascending limb of the loop of Henle, with loss of function of NKCC2, ROMK, Barttin, CLC-Kb or CLC-Ka; and associated with mutations in *SLC12A1*, *KCNJ1*, *BSND* (with sensorineural hearing loss), *CLCNKB*, and *CLCKA* respectively (50). Very rarely, mutations in *MAGED2* have been reported in an X-linked presentation of antenatal Bartter syndrome, which affects the functioning and expression of NKCC2 and NCC (51). Gitelman syndrome is also characterised by hypocalciuria and hypomagnesaemia. A single mutation can result in a mild phenotype with fatigue and cramps. Gitelman syndrome reduces the function of the thiazide sensitive sodium-chloride symporter (NCC), located in the distal convoluted tubule, and is due to mutations of *SLC12A3* (NCC) or *CLCNKB* (CLC-Kb) (52). It is worth noting that those with *KCNJ1* mutations can present with transient hyperkalaemia; and *CLCNKB* and *SLC12A3* hypomagnesaemia (24).

Gitelman syndrome can be distinguished from Bartter syndrome as it tends to demonstrate hypocalciuria (urine calcium:creatinine ratio <0.2 mol/moL) and dilute urine, whereas Bartter syndrome typically presents with hypocalcaemia and urine calcium:creatinine ratio >0.2 mol/moL. Gitelman is also more associated with hypomagnesaemia, but this can occur in Bartter too (27). Bartter syndrome presents in the antenatal period or milder phenotypes, e.g., classical Bartter, can present at any age but most commonly childhood (22). Gitelman syndrome is milder, but has very marked phenotypic variation, therefore

severe cases do exist presenting earlier, however it can present later with some cases being relatively asymptomatic (22). Some cases of Gitelman can present with hypertension, adding to the possible confusion (22).

Clinical phenotype is inadequate to differentiate Bartter and Gitelman syndromes due to the overlap. However, a diuretic test or genetic testing can help confirm the diagnosis (22,28). The diuretic test works on the principle that a loop diuretic will have no effect in Bartter syndrome cases, as NKCC function is already disrupted, and thiazides have no effect in Gitelman as NCC is similarly affected (22,25). Urine sodium and chloride is measured on spot urines, 6 hours post administration, but there are various limitations (including the need to stop other therapies to perform the test), and the test is not always entirely diagnostic (22). Genetics, although probably the gold standard, can be complicated by the range of mutations described, but will continue to improve as techniques and knowledge improves (22).

It is worth noting that aminoglycoside antibiotics simulate a transient Bartter syndrome, causing metabolic alkalosis and hypomagnesaemia, sometimes known as acquired Bartter syndrome (22,53). Very rarely, acquired Gitelman syndrome has been described mostly secondary to Sjögren syndrome, and thought to be due to antibodies to NCC, as has Bartter syndrome (54).

SESAME

The seizures, sensorineural deafness, ataxia, mental retardation, and electrolyte imbalance syndrome or SESAME (also known as EAST, for epilepsy, ataxia, sensorineural deafness and tubulopathy, syndrome), is caused by a mutation in the *KCNJ10* gene for an inward rectifying potassium channel (Kir4.1). This loss of function results in salt loss and hence stimulation of aldosterone release. Magnesium renal wasting and hypomagnesaemia also occurs, rather similar to Gitelman (55).

Autosomal dominant familial hypocalcaemia

Autosomal dominant familial hypocalcemia, affecting the calcium receptor gene *CASR*, causes a hypochloremic, hypokalaemic, metabolic alkalosis. This condition can be confused with Bartter syndrome as it presents with hypocalaemia (22). The dominant inheritance can help differentiate between the recessive Bartter syndrome, and PTH will also be inappropriately low (22).

Chloride losing diarrhoea

Other rare causes of hypochloremic alkalosis are chloride

losing diarrhoea caused by CF or congenital chloride diarrhoea (CCD). CCD is caused by defects in the Cl^-/HCO_3^- anion exchanger because of 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 (56). Patients with CCD are alkalotic as HCO_3^- cannot be excreted (57). CF is caused by a mutation in the CF transmembrane conductance regulator (*CFTR*) gene, and is also linked with hyponatremia and hypochloraemia, due to hyperaldosteronism, with alkalosis, in order to replace the salt lost in sweat (58,59).

Dents disease

Dents disease is an X-linked disorder caused by mutations in *CLCN5* (type 1) and *OCRL1* (type 2), causing proteinuria, hypercalciuria, nephrolithiasis, and rickets, among other things (60). *CLCN5* encodes the chloride channel protein 5 (CLCL-5) that exchanges H^+ for Cl^- ions in the proximal tubule. A few patients can manifest hypochloraemia, metabolic alkalosis, and hypokalaemia) (22,61).

Conclusions

The investigation of alkalosis can be challenging, with many conditions affecting the homeostasis. A correctly interpreted arterial blood gas can give clear indication of where the problem may have originated, and if that test is not available, we have presented how to work through a raised bicarbonate result. The diagnostic algorithms attached to this article will help the reader to systematically consider causes of alkalosis. However, we appreciate that each patient case is different and it may be appropriate to skip to steps later in the algorithms, refer to other algorithms (e.g., acidosis within this series), or even miss out steps entirely. These algorithms cannot replace specialist knowledge, experience and local guidelines. Instead, they should act as diagnostic aids when assessing alkalotic patients.

Acknowledgments

Footnote

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Table S1 Narrative Review checklist

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:	Alkalosis, Diagnosis, Investigation, Causes, Aetiology, Paediatrics, Pregnancy, Respiratory, Metabolic
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.)	George T. Allen and Alexa R. 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