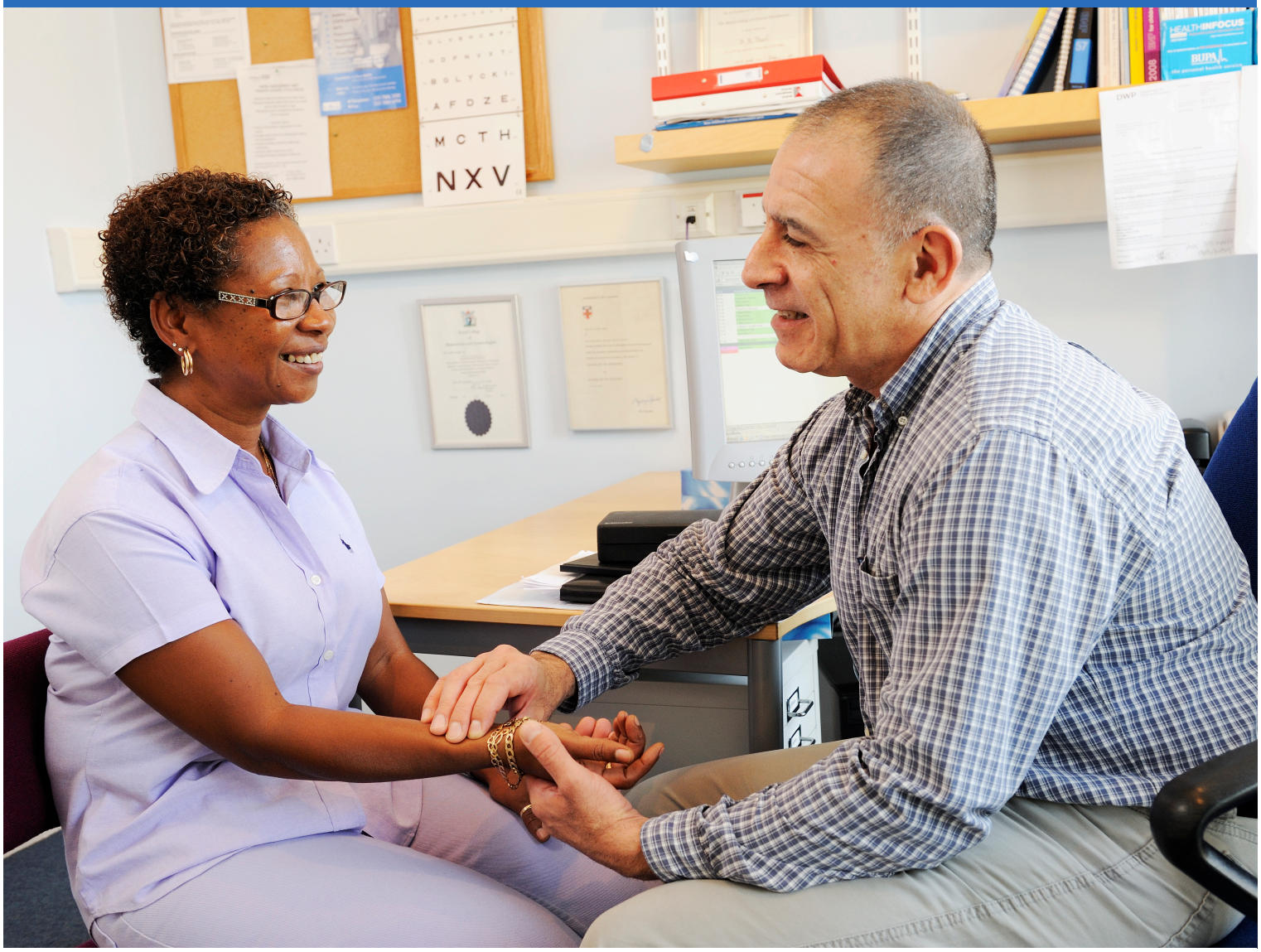
BMJ Best Practice

Assessment of metabolic alkalosis

Straight to the point of care



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Summary

Definition

Metabolic alkalosis is indicated by an increase in plasma bicarbonate (HCO_3) level. Arterial pH >7.45 defines alkalosis.

It is the consequence of disorders that cause either a loss of hydrogen ions from the body or an increase in plasma HCO_3. The severity of alkalosis depends on the severity of underlying disorder; it may be more severe if both metabolic and respiratory alkalosis are present.

Pathophysiology

The main mechanisms involved can be one, or a combination, of following:

- Loss of hydrogen ions from the body. Hydrogen ions can be lost from the body either through the gastrointestinal tract or through the kidneys. In the body, hydrogen ions may shift from the extracellular fluid into the cells. If the loss of hydrogen ions exceeds production by the diet and metabolism, the serum HCO_3 level increases, leading to metabolic alkalosis.[1] Loss of hydrogen ions through the stomach and kidneys is accompanied by the production of HCO_3.
- Administration of HCO_3, addition of HCO_3-generating substances, or intake of HCO_3 or substances (citrate, acetate, or lactate) that increase HCO_3 production in excess of hydrogen ion production will lead to metabolic alkalosis. This is usually compensated by the kidneys with normal function by renal excretion of HCO_3.[1]
- Severe circulating volume contraction. This leads to loss of extracellular fluid and relative increase in HCO_3 concentration.

Metabolic alkalosis generally requires an initiation factor that starts the process and a maintenance factor that continues the imbalance by preventing renal excretion of excess HCO_3. Sometimes, the same factor may be responsible for both initiation and maintenance.[2] [3]

Aetiology

The differential diagnosis of metabolic alkalosis divides patients into those that have volume depletion (also called chloride-responsive metabolic alkalosis) and those that do not have volume depletion (also called chloride-resistant metabolic alkalosis).

Chloride-resistant metabolic alkalosis

With hypertension:[2] [4] [5] [6] [7]

- Primary hyperaldosteronism
- Secondary hyperaldosteronism, for example, renin-producing tumour
- Renal artery stenosis
- Cushing's syndrome
- Liquorice ingestion
- Tobacco chewing
- Apparent mineralocorticoid excess
- Liddle's syndrome: autosomal-dominant inheritance, early onset hypertension, hypokalaemic metabolic alkalosis, low plasma renin activity, and suppressed aldosterone secretion.[4]

No hypertension:[8] [9] [10] [11] [12] [13]

- Bartter's syndrome: autosomal-recessive inheritance, hypokalaemic metabolic alkalosis, raised plasma renin activity and hyperaldosteronism, normal blood pressure (BP), deranged prostaglandin metabolism, and increased urinary chloride excretion
- Gitelman's syndrome: autosomal-recessive inheritance, hypokalaemic metabolic alkalosis, hypocalciuria, and hypomagnesaemia
- Current loop or thiazide diuretic therapy
- Profound potassium depletion
- Hypercalcaemia of non-hyperparathyroid aetiology
- Post-starvation refeeding syndrome
- Transfusion of blood products (sodium citrate).

Chloride-responsive metabolic alkalosis

Gastrointestinal causes:[2] [5][14][15] [16]

- Vomiting
- Gastric drainage
- Villous adenoma of colon (usually leads to normal anion gap metabolic acidosis; however, some of these tumors secrete chloride, leading to metabolic alkalosis)
- Congenital chloride diarrhoea (rare congenital syndrome due to a defect in large bowel chloride absorption, which leads to chronic diarrhoea with stool fluid rich in chloride)
- Cystic fibrosis.

Renal causes:[2] [5]

- Post-diuretic therapy
- Post-hypercapnia.

Exogenous alkali intake:[2] [5] [17]

- Bicarbonate administration
- Milk-alkali syndrome.

Urgent considerations

(See **Differentials** for more details)
Severe metabolic alkalosis (arterial pH >7.6) requires immediate attention and treatment, as it may lead to life-threatening seizures and ventricular arrhythmias.

Arterial pH is rapidly reduced by controlled hypoventilation, using sedation and mechanical ventilation. Volume depletion can be corrected with normal saline, and electrolyte abnormalities such as hypokalaemia should also be corrected.[18] [19]

Alternative treatments, such as giving hydrogen chloride (HCl) or ammonium chloride, are indicated if normal saline is contraindicated (e.g., in cases of fluid overload) but have a high risk of complications (haemolysis and tissue necrosis with HCl and ammonia toxicity with ammonium chloride).[2] HCl solution can be given over a period of 6 to 8 hours through a central vein.

In presence of fluid overload, the diuretic acetazolamide, a carbonic anhydrase inhibitor that acts by decreasing the reabsorption of sodium bicarbonate ($NaHCO_3$) in the proximal tubule, can be used.

Haemodialysis with a low bicarbonate bath may be needed to correct severe metabolic alkalosis in patients with advanced kidney failure.

Approach

Systematic evaluation of acid-base status of the patient provides insight into the underlying medical problem. The differential diagnosis of the cause of metabolic alkalosis can be narrowed down by clinical evaluation and laboratory investigation.

Clinical evaluation

The evaluation of the patient with metabolic alkalosis begins with ascertaining whether there is volume depletion leading to chloride depletion.

A history of vomiting, nasogastric suction or drainage, diuretic use, cystic fibrosis, hypercapnia, or excessive bicarbonate (HCO_3) or alkali intake should be sought.

Patients may present with tingling, muscle cramps, weakness, cardiac arrhythmias, and/or seizures.[5] [20] [21] Some of these symptoms may be due to a decrease in circulating ionised calcium, which results from the greater binding to albumin when pH is high. It is important to note that patients may develop serious or even fatal arrhythmias and/or seizures without preceding symptoms.

There are no specific signs of metabolic alkalosis, but examination may provide clues to the underlying cause.

Occasionally, compensatory metabolic alkalosis is an incidental finding in patients with chronic respiratory acidosis.

Investigations

These clinical conditions with acid-base disorders can be effectively assessed by a stepwise pathophysiological approach.

Arterial blood gas (ABG) and urinary chloride concentration measurements should be requested and the data interpreted using the following steps:

1. Determine the disturbance in pH:
    - Arterial pH indicates the ongoing disturbance -- alkalosis versus acidosis.
    - At sea level the normal pH is 7.42±0.02.
    - Increase in arterial pH >7.45 suggests that the major ongoing disturbance is alkalosis.
2. Identify the primary disorder:
    - To determine the primary disorder, examine the directional changes of serum HCO_3 and arterial partial pressure of carbon dioxide ($PaCO_2$) from the normal and their relation with change in arterial pH.
    - If the pH is high and HCO_3 is high (>24 mmol/L or 24 mEq/L), then the primary disorder is metabolic alkalosis.
3. Assess compensation in response to the primary disorder:
    - With simple metabolic alkalosis, the normal adaptive respiratory response increases the arterial $PaCO_2$ by 0.25 to 1 times the increase in serum HCO_3.

4. Determine the type of metabolic alkalosis:
    - In general, the urinary chloride concentration is >20 mmol/L (20 mEq/L) in patients who do not respond to volume expansion with normal saline (chloride-resistant metabolic alkalosis), whereas it is <10 mmol/L (10 mEq/L) in those who do respond to volume expansion (chloride-responsive metabolic alkalosis).[22]
5. Further investigations to determine the underlying cause of metabolic alkalosis are performed based on the history and examination findings.

Further investigation in chloride-resistant metabolic alkalosis

Serum potassium is a useful first test in some conditions, including primary hyperaldosteronism, apparent mineralocorticoid excess, Liddle's syndrome, Bartter's syndrome, Gitelman's syndrome, profound potassium depletion, and liquorice ingestion.

Serum aldosterone and serum renin activity should be measured in patients with hypertension and a history compatible with primary hyperaldosteronism, secondary hyperaldosteronism, renal artery stenosis, apparent mineralocorticoid excess, or Liddle's syndrome.

Further investigations in hypertensive patients are indicated as follows:

- If there are clinical features of Cushing's syndrome, diagnosis is confirmed with 24-hour urinary free cortisol and a corticotropin-releasing hormone stimulation test with dexamethasone suppression test.[7]
- 24-hour urine aldosterone is measured in primary hyperaldosteronism.
- 24-hour urinary free cortisol to cortisone ratio is useful in conjunction with the history in confirming liquorice ingestion.
- Renal artery stenosis should be confirmed with duplex renal ultrasound.

In the absence of hypertension, but with features in the history or examination suggestive of Bartter's syndrome or Gitelman's syndrome, measurement of serum potassium, as well as urinary calcium and chloride, is indicated. Serum magnesium is low in Gitelman's syndrome, differentiating it from Bartter's syndrome.

Further tests in non-hypertensive patients are as follows:

- Serum calcium and parathyroid hormone are indicated if hypercalcaemia of non-hyperparathyroid aetiology is a potential diagnosis.
- Serum phosphate should be monitored in post-starvation refeeding syndrome.
- A urinary drug screen would detect any current diuretic therapy if not evident from the history. It is not routinely done but can be performed if the cause of the alkalosis is not readily apparent.

Further investigation in chloride-responsive metabolic alkalosis

Urinary and faecal chloride should be measured in patients with excessive gastrointestinal secretion losses (vomiting, gastric drainage, villous adenoma of colon, congenital chloride diarrhoea).

A sweat test and genetic testing are indicated if cystic fibrosis is suspected.

Diagnosis is clinical in cases of post-diuretic therapy, HCO_3 administration, and milk-alkali syndrome, and no further testing is required.

In the scenario of post-hypercapnia, raised $PaCO_2$ would have been detected on the ABG analysis.

Differentials overview

Common
Current diuretic therapy
Gastric secretion loss
Post-diuretic therapy
Post-hypercapnia
Bicarbonate administration
Milk-alkali syndrome
Uncommon
Primary hyperaldosteronism
Secondary hyperaldosteronism
Renal artery stenosis
Cushing's syndrome
Liquorice ingestion
Tobacco chewing
Apparent mineralocorticoid excess
Liddle's syndrome
Bartter's syndrome
Gitelman's syndrome
Profound potassium depletion
Hypercalcaemia of non-hyperparathyroid aetiology
Post-starvation refeeding syndrome
Transfusion of blood products (sodium citrate)

Uncommon

Villous adenoma

Congenital chloride diarrhoea

Cystic fibrosis

Differentials

Common

◊ Current diuretic therapy

History	Exam	1st Test	Other tests
prescribed or illicit use of loop and thiazide diuretics	no specific examination findings	»**clinical diagnosis:** based on history of diuretic use	»**urinary drug screen:** positive for diuretics Not routinely done but can be performed if the cause of the alkalosis is not readily apparent.

◊ Gastric secretion loss

History	Exam	1st Test	Other tests
vomiting, gastric drainage	dry mouth, decreased skin turgor	»**urinary chloride:** low (<10 mmol/L or 10 mEq/L)	

◊ Post-diuretic therapy

History	Exam	1st Test	Other tests
discontinuation of diuretic use (loop and thiazide diuretics)	no specific examination findings	»**clinical diagnosis:** no specific tests recommended	

◊ Post-hypercapnia

History	Exam	1st Test	Other tests
when chronic hypercapnia is rapidly corrected with mechanical ventilation, the patient continues to have high plasma HCO_3 levels for some time as renal correction takes a few hours	no specific examination findings	»**ABG:** raised $PaCO_2$ Respiratory failure on initial ABG.	

DIAGNOSIS

Common

◊ Bicarbonate administration

History	Exam	1st Test	Other tests
ingestion of alkali antacids or milk for gastro-oesophageal reflux disease or overtreatment of metabolic acidosis	no specific examination findings	»**clinical diagnosis:** no specific tests recommended	

◊ Milk-alkali syndrome

History	Exam	1st Test	Other tests
excessive intake of absorbable antacids, milk, or calcium supplements	no specific examination findings	»**clinical diagnosis:** no specific tests recommended	

Uncommon

◊ Primary hyperaldosteronism

History	Exam	1st Test	Other tests
muscular weakness, paraesthesia, headache, polyuria, polydipsia	raised BP	»**serum potassium:** low »**serum aldosterone:** high Normal values: High salt diet -- supine: 83 to 277 picomol/L (3 to 10 nanograms/decilitre); upright: 139 to 832 picomol/L (5 to 30 nanograms/decilitre). Low salt diet -- supine: 333 to 999 picomol/L (12 to 36 nanograms/decilitre); upright: 472 to 3800 picomol/L (17 to 137 nanograms/decilitre).	»**24-hour urine aldosterone:** >55 nanomol/24 hours (>20 micrograms/24 hours) Patient must have high salt intake during the evaluation.

Uncommon

◊ Primary hyperaldosteronism

History	Exam	1st Test	Other tests
		»**serum renin activity:** low Normal values: High sodium diet -- supine: 0.2 to 2.3 nanograms/mL/hour; standing: 1.3 to 4 nanograms/mL/hour. Low sodium diet -- standing: 4 to 7.7 nanograms/mL/hour.	

◊ Secondary hyperaldosteronism

History	Exam	1st Test	Other tests
hypertension, heart failure, liver failure, nephrotic syndrome	signs of underlying disorder such as raised jugular venous distension, peripheral oedema, or ascites	»**serum aldosterone:** high Normal values: High salt diet -- supine: 83 to 277 picomol/L (3 to 10 nanograms/decilitre); upright: 139 to 832 picomol/L (5 to 30 nanograms/decilitre). Low salt diet -- supine: 333 to 999 picomol/L (12 to 36 nanograms/decilitre); upright: 472 to 3800 picomol/L (17 to 137 nanograms/decilitre). »**serum renin activity:** high Normal values: High sodium diet -- supine: 0.2 to 2.3	

Uncommon

◊ Secondary hyperaldosteronism

History	Exam	1st Test	Other tests
		nanograms/mL/hour; standing: 1.3 to 4 nanograms/mL/hour. Low sodium diet -- standing: 4 to 7.7 nanograms/mL/hour. Level over 50 nanograms/mL/hour is suggestive of renin-producing tumour.	

◊ Renal artery stenosis

History	Exam	1st Test	Other tests
uncontrolled hypertension, presents in young women (<40 years of age) or patients >50 years of age with risk factors for cardiovascular disease	raised BP	»**serum aldosterone:** high Normal values: High salt diet -- supine: 83 to 277 picomol/L (3 to 10 nanograms/decilitre); upright: 139 to 832 picomol/L (5 to 30 nanograms/decilitre). Low salt diet -- supine: 333 to 999 picomol/L (12 to 36 nanograms/decilitre); upright: 472 to 3800 picomol/L (17 to 137 nanograms/decilitre). »**serum renin activity:** high Normal values: High sodium diet -- supine: 0.2 to 2.3 nanograms/mL/hour;	»**duplex renal ultrasound:** high flow through stenotic lesion High sensitivity and specificity.[23]

Uncommon

◊ Renal artery stenosis

History	Exam	1st Test	Other tests
		standing: 1.3 to 4 nanograms/mL/hour. Low sodium diet -- standing: 4 to 7.7 nanograms/mL/hour.	

◊ Cushing's syndrome

History	Exam	1st Test	Other tests
weakness, obesity, diabetes mellitus, hypertension, backache, menstrual irregularities	central obesity, facial plethora, proximal myopathy, hirsutism, abdominal striae, acne, bruises	»**late-night salivary cortisol:** raised »**1 mg overnight dexamethasone suppression test:** morning cortisol >50 nanomoles/L (>1.8 micrograms/dL) Should be a first-line test in any patient with suspected Cushing's syndrome, except those taking drugs affecting dexamethasone metabolism (phenytoin, carbamazepine, rifampicin [rifampin], and cimetidine). »**24-hour urinary free cortisol:** >828 nanomoles/24 hours (>300 micrograms/24 hours) considered diagnostic At least two 24-hour urinary free cortisol samples should be collected to increase diagnostic accuracy.[7]	

Uncommon

◊ Liquorice ingestion

History	Exam	1st Test	Other tests
liquorice ingestion, may be included in complementary medical therapies such as antacids	no specific examination findings	»**serum potassium:** low »**24-hour urinary free cortisol to cortisone ratio:** high Normal ratio 0.3 to 0.5.[24]	

◊ Tobacco chewing

History	Exam	1st Test	Other tests
tobacco chewing	no specific examination findings	»**clinical diagnosis:** no investigation required	

◊ Apparent mineralocorticoid excess

History	Exam	1st Test	Other tests
positive family history (autosomal-recessive pattern), faltering growth, severe hypertension in childhood, renal failure	raised BP	»**serum aldosterone:** low Normal values: High salt diet -- supine: 83 to 277 picomol/L (3 to 10 nanograms/decilitre); upright: 139 to 832 picomol/L (5 to 30 nanograms/decilitre). Low salt diet -- supine: 333 to 999 picomol/L (12 to 36 nanograms/decilitre); upright: 472 to 3800 picomol/L (17 to 137 nanograms/decilitre). »**serum renin activity:** low Normal values:	»**serum potassium:** low

Uncommon

◊ Apparent mineralocorticoid excess

History	Exam	1st Test	Other tests
		High sodium diet -- supine: 0.2 to 2.3 nanograms/mL/hour; standing: 1.3 to 4 nanograms/mL/hour. Low sodium diet -- standing: 4 to 7.7 nanograms/mL/hour.	

◊ Liddle's syndrome

History	Exam	1st Test	Other tests
positive family history (autosomal-dominant pattern), hypertension in early childhood	raised BP	»**serum aldosterone:** low Normal values: High salt diet -- supine: 83 to 277 picomol/L (3 to 10 nanograms/decilitre); upright: 139 to 832 picomol/L (5 to 30 nanograms/decilitre). Low salt diet -- supine: 333 to 999 picomol/L (12 to 36 nanograms/decilitre); upright: 472 to 3800 picomol/L (17 to 137 nanograms/decilitre). »**serum renin activity:** low Normal values: High sodium diet -- supine: 0.2 to 2.3 nanograms/mL/hour; standing: 1.3 to 4 nanograms/mL/hour.	»**serum potassium:** low

Uncommon

◊ Liddle's syndrome

History	Exam	1st Test	Other tests
		Low sodium diet -- standing: 4 to 7.7 nanograms/mL/hour.	

◊ Bartter's syndrome

History	Exam	1st Test	Other tests
positive family history (autosomal recessive), usually presents in children, polyuria, dehydration, mimics loop diuretic use	normal to low BP, rarely associated with sensorineural defects	»**urinary chloride:** high (>20 mmol/L or 20 mEq/L) In the absence of diuretic use. »**urinary calcium:** high Normal range 100 to 300 mg/day.	»**serum potassium:** low

◊ Gitelman's syndrome

History	Exam	1st Test	Other tests
positive family history (autosomal recessive), milder symptoms than Bartter's syndrome, mimics thiazide diuretic use	normotensive	»**urinary chloride:** high (>20 mmol/L or 20 mEq/L) In the absence of diuretic use. »**urinary calcium:** low Normal range 100 to 300 mg/day.	»**serum potassium:** low »**serum magnesium:** low

Profound potassium depletion

History	Exam	1st Test	Other tests
diarrhoea or diuretic use (other medications that cause hypokalaemia include beta-agonists, theophylline, or insulin),	no specific examination findings	»**serum potassium:** low Less than 2 mmol/L.	

Uncommon

Profound potassium depletion

History	Exam	1st Test	Other tests
muscular weakness, fatigue, muscle cramps			

◊ Hypercalcaemia of non-hyperparathyroid aetiology

History	Exam	1st Test	Other tests
constipation, polyuria	severe hypercalcaemia can cause stupor	»**serum calcium:** high Less than 0.5 mmol/L (2 mg/decilitre).	»**PTH:** normal or low

◊ Post-starvation refeeding syndrome

History	Exam	1st Test	Other tests
history of anorexia nervosa, alcohol misuse, post-operative patients, or patients who are fed through nasogastric or percutaneous endoscopic gastrostomy tubes are also at risk	no specific examination findings	»**serum phosphate:** low Severe hypophosphatasaemia usually occurs within several days of starting to feed.[13]	

◊ Transfusion of blood products (sodium citrate)

History	Exam	1st Test	Other tests
transfusion of >10 units of blood (sodium citrate is metabolised to bicarbonate [HCO_3])	no specific examination findings	»**clinical diagnosis:** no specific tests recommended Need to exclude other causes of metabolic alkalosis in critically ill patients.	

Uncommon

◊ Villous adenoma

History	Exam	1st Test	Other tests
severe diarrhoea (secretory diarrhoea syndrome)	dry mouth, decreased skin turgor	»**urinary chloride:** low (<10 mmol/L or 10 mEq/L)	»**faecal chloride:** high Only indicated if histoy of diarrhoea.

◊ Congenital chloride diarrhoea

History	Exam	1st Test	Other tests
may be positive family history (autosomal recessive); history of polyhydramnios, history of premature birth; voluminous watery stools from a few weeks of age	dry mouth, decreased skin turgor; faltering growth	»**urinary chloride:** low (<10 mmol/L or 10 mEq/L) »**faecal chloride:** high	

◊ Cystic fibrosis

History	Exam	1st Test	Other tests
typically known diagnosis; variable phenotype including faltering growth, recurrent pneumonia; chronic obstructive lung disease, diarrhoea, dehydration in hot weather, and infertility; rarely presents as metabolic alkalosis	depends on phenotype; includes poor weight gain, wheeze, thick sputum production, clubbing, hepatomegaly	»**sweat test:** sweat chloride value >60 mmol/L (60 mEq/L)	»**genetic testing:** CFTR gene mutation Most laboratories will perform an initial 'screen' for the most common CFTR mutations. If two common mutations are not found, most laboratories have an option for sequencing more of the CFTR gene or the entire CFTR gene.

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Please note that recommended formulations and doses may differ between drug databases drug names and brands, drug formularies, or locations. A local drug formulary should always be consulted for full prescribing information.

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BMJ accepts no responsibility for misinterpretation of numbers which comply with this stated numerical separator standard.

This approach is in line with the guidance of the International Bureau of Weights and Measures Service.

Figure 1 – BMJ Best Practice Numeral Style

5-digit numerals: 10,000

4-digit numerals: 1000

numerals < 1: 0.25

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