Potassium (serum, plasma, blood)

1 Name and description of analyte

1.1 Name of analyte
Potassium (K^+)

1.2 Alternative names
None

1.3 NMLC code
To follow

1.4 Description of analyte
Potassium is an alkaline metal, atomic number 19. It occurs in the body primarily as free cations. It is the most abundant cation in the body, with 98% being intracellular.

1.5 Function of analyte
The intracellular to extracellular concentration ratio of potassium determines resting membrane potential and is critical to neural and muscle cell activity. The ratio is controlled by cellular uptake via the Na^+,K^+-APTase pump on cell membranes and passive diffusion out of cells. Distribution across cell membranes is influenced by numerous factors e.g. hormones, principally insulin and catecholamines, acid-base status and extracellular tonicity.
Aldosterone is the major regulator of body stores of potassium. Aldosterone exerts its effects on potassium excretion in the distal renal tubules. Aldosterone secretion release is subject to feedback control by potassium, independently of the effect of renin: hyperkalaemia stimulates it; hypokalaemia inhibits it.

2 Sample requirements and precautions

2.1 Medium in which measured
1. Potassium can be measured in serum, plasma (lithium heparin) or heparin-anticoagulated whole blood. Potassium is released from platelets during clotting. Therefore, plasma and whole blood concentrations are 0.1–0.7 mmol/L lower than those in serum.
2. Potassium can also be measured in urine (random or 24 h). No preservatives are required.

2.2 Precautions re sampling, handling etc.
Haemolysis: haemolysis causes release of potassium from erythrocytes leading to falsely elevated results. The effect is not predictable. Haemolysis cannot be detected in whole blood samples.
Delayed separation: a delay in separation of the cells from serum or plasma eventually causes a misleading increase in [K^+]; so, too, does leaving serum in contact with cells after centrifugation and re-centrifuging gel separator tubes. Temperature is an important factor: cold storage of whole blood samples before separation will inhibit glycolysis and the energy-dependent Na^+,K^+-ATPase will not maintain the transcellular potassium gradient. This will cause false increases in [K^+]

owing to leakage from cells. Conversely, storage above room temperature will initially cause falsely decreased [K^+] due to increased Na^+,K^+-ATPase activity before glucose is exhausted and [K^+] rises.
Thrombocythaemia: potassium is released from platelets leading to falsely raised [K^+]; a lithium heparin plasma sample should be used for potassium measurement in patients with thrombocythaemia.
Leukocytosis: this initially causes a decrease in [K^+] as a result of glycolysis and augmented Na^+,K^+-ATPase activity: when a leukocytosis is present, measurement should be made on a lithium heparin plasma sample *immediately* transported on ice to the laboratory; alternatively, whole blood should be measured *immediately* on a point of care analyser with a potassium electrode. Once glucose substrate is exhausted, [K^+] increases owing to leakage from cells.
Fist clenching: this can cause potassium efflux from cells, leading to a falsely raised [K^+].
Contamination: contamination with K-EDTA may occur when blood is poured from one collection tube to another.

3 Summary of clinical uses and limitations of measurements

3.1 Uses

1. Diagnosis of hypokalaemia and hyperkalaemia.
2. Monitoring patients at risk of developing hypokalaemia or hyperkalaemia (see section 7).
3. Calculation of the anion gap in acid-base disturbances.
4. Calculation of the osmolal gap.

3.2 Limitations

Measurement of potassium cannot provide information as to the cause of either hyper- or hypokalaemia, nor is it a reliable indicator of total body potassium.
Note that diagnostic and action values for [K^+] in this article refer to measurements in serum unless stated otherwise.

4 Analytical considerations

4.1 Analytical methods

Many techniques are available to measure potassium including:, ion-selective electrodes (ISE), atomic absorption, spectrophotometry and flame photometry. Most laboratories and point of care testing (PoCT) devices use ion-selective electrode methods, with the other methods employed almost exclusively by large reference and research laboratories.

Potassium electrodes have liquid ion-exchange membranes consisting of an inert solvent in which neutral carrier substances, e.g. valinomycin, are dissolved. The electrode membrane is in contact with both the test solution and an internal filling solution. The internal filling solution contains potassium ions at a fixed concentration. Because of the particular nature of the membrane, the test ions will closely associate with the membrane on each side. The membrane EMF is determined by the difference in concentration of potassium ions in the test solution and the internal filling solution. The EMF develops according to the Nernst equation for a specific ion in solution.

4.2 Reference method
Flame photometry

4.3 Reference material
Potassium chloride (Standard Reference Material (SRM) 918).

4.4 Interfering substances
None

4.5 Sources of error:
Sources of error with ISEs are:

- lack of selectivity
- protein coating of the ion-selective membrane
- contamination of the membrane by competing ions.

5 Reference intervals and variance

5.1.1 Reference interval (adults):
serum 3.5–5.3 mmol/L

5.1.2 Reference intervals (others):
The following ranges are for plasma samples
neonates: 3.4–6.0 mmol/L
infants: 3.5–5.7 mmol/L
children 1–16 y: 3.5–5.0 mmol/L

5.1.3 Extent of variation

5.1.3.1 Interindividual CV: 4.4%

5.1.3.2 Intraindividual CV: 5.1%

5.1.3.3 Index of individuality: 1.16

5.1.3.4 CV of method: <2.4%

5.1.3.5 Critical difference: 14%

5.1.4 Sources of variation
Consumption of foods high in potassium may contribute to variations in its concentration. Also, $[K^+]$ may vary in relation to a high carbohydrate meal as this stimulates insulin release and thus cellular uptake of potassium. An acute but transient rise in plasma $[K^+]$ occurs during and immediately following exercise.

6 Clinical uses of measurement and interpretation of results

6.1 Uses and interpretation
1. Diagnosis of hypokalaemia and hyperkalaemia
Hypo- or hyperkalaemia may be suspected on clinical grounds e.g. cardiac arrhythmia or ECG changes. In many cases, however, the diagnosis is an incidental finding when potassium is measured on a 'urea and electrolytes' or 'renal function' profile. Potassium should also be measured when investigating conditions associated with with hypo- or hyperkalaemia (see section 7) and when monitoring patients on drugs known to cause hypo- or hyperkalaemia (see section 7).
2. During treatment of hypo- and hyperkalaemia.
3. Calculation of the anion gap in acid-base disturbances
The *serum* anion gap is calculated as:
$([Na^+] + [K^+]) - ([Cl^-] + [HCO_3^-])$

The normal anion gap is 10–18 mmol/L. A high anion gap can help elucidate the cause of a metabolic acidosis.
The *urine* anion gap is calculated as:
$([Na^+] + [K^+]) - ([Cl^-])$
In a patient with hyperchloraemic (normal serum anion gap) metabolic acidosis, a negative urine anion gap suggests gastrointestinal loss of bicarbonate (e.g. diarrhoea). A positive urine anion gap suggests impaired renal distal acidification (i.e. renal tubular acidosis).
4. Calculation of osmolarity and the osmolal gap
Osmolarity is calculated from a formula that sums the molar concentrations of the solutes that, under normal circumstances, contribute nearly all of the osmolality of the sample. There are many variations of the formula, one of which is:
$1.89[Na^+] + 1.38[K^+] + 1.03[urea] + 1.08[glucose] + 7.45$
The osmolal gap is the measured osmolality minus the calculated osmolarity. The normal value is <10 mmol/L. A raised gap suggests the presence of abnormal osmotically active substance(s) e.g. ethanol, methanol, ethylene glycol.

6.2 Confounding factors: none

7 Causes of abnormal results

7.1 High values

7.1.1 Causes

1. Spurious
    - *In vitro* haemolysis: the mechanical disruption of erythrocytes causes release of potassium and can be due for example to traumatic venepuncture, use of a small needle, transport via an airtube system before sample has clotted.
    - Delayed separation: a delay in separation of the sample causes leakage of potassium from cells. Potassium may begin to increase after 1 h in whole blood. This is exacerbated by low temperature: cold storage of whole blood samples before separation will inhibit glycolysis and the energy-dependent Na^+,K^+-ATPase will not maintain the transcellular potassium gradient. Some potassium leaking from cells remains in the extracellular fluid, causing an increase in concentration.
    - Thrombocythaemia: potassium is released from platelets.
    - Leukocytosis: $[K^+]$ increases owing to leakage from white blood cells and increased white blood cell fragility.
    - Fist clenching: this can cause potassium efflux from cells, leading to a spuriously raised concentration.
    - Contamination: use of K-EDTA collection tube; specimen collection from vein into which potassium is being infused.
    - Genetic: familial pseudohyperkalaemia (uncommon).
2. Potassium redistribution
    - Drugs
        - β-blockers
        - suxamethonium
        - hyperosmolar solutions.
    - Tissue injury or necrosis
        - rhabdomyolysis

    - tumour lysis syndrome
    - severe burns
    - severe trauma
  - Insulin deficiency with hyperglycaemia
  - Metabolic acidosis
  - Hyperkalaemic periodic paralysis.
3. Increased potassium intake (including iatrogenic)
  - Excessive dietary intake (uncommon).
  - Use of salt substitutes
  - Blood transfusion.
  - Over-replacement i.e. potassium supplements, IV fluids containing potassium including parenteral nutrition
  - Herbal medicines.
4. Decreased potassium excretion
  - Renal failure
  - Hypoaldosteronism or lack of renal tubular response to aldosterone
    - adrenal insufficiency
    - congenital adrenal hyperplasia e.g. 21-hydroxylase deficiency 3-β hydroxysteroid dehydrogenase deficiency
    - hyporeninaemic hypoaldosteronism (type 4 renal tubular acidosis) (e.g. chronic kidney disease, diabetic nephropathy, non steroidal anti-inflammatory drugs (NSAIDs).
    - pseudohypoaldosteronism
      - type 1a: loss of function mutation of mineralocortocoid receptor
      - type 1b: loss of function mutation of epithelial sodium channel
    - conditions causing end-organ resistance to aldosterone e.g. sickle cell anaemia, systemic lupus erythematosus (LE), amyloidosis, obstructive nephropathy
    - drugs that reduce aldosterone secretion:
      - angiotensin converting enzyme inhibitors (ACEI)
      - angiotensin receptor blockers (ARBs)
      - NSAIDs
      - heparin
      - antifungals
      - ciclosporin
      - tacrolimus
    - drugs that block aldosterone binding to the mineralocorticoid receptor:
      - spironolactone
      - eplerenone
      - drospirenone
    - drugs that inhibit activity of epithelial sodium channel:
      - amiloride
      - triamterene
      - trimethoprim
      - pentamidine.
  - Decreased urine flow rate or sodium delivery to the distal tubule
    - severe volume contraction
    - rare genetic disorders e.g. pseudohypoaldosteronism type II (Gordon's syndrome).

7.1.2 Investigation

In the first instance, it is important to exclude spurious hyperkalaemia. A check should be made for the presence of haemolysis (many modern laboratory analysers produce a haemolysis index, which has replaced visual inspection), a delay in transit time, and the presence of thrombocytosis or leucocytosis on the full blood count. If either of the latter is present, a lithium heparin sample should be requested for repeat potassium measurement. Very low concentrations of calcium and magnesium and low alkaline phosphatase activity suggest EDTA contamination.

The investigation of the cause of true hyperkalaemia should initially include a review of urea and creatinine results for evidence of renal failure. The medical history may reveal possible causes of hyperkalaemia e.g. drugs, autoimmune disease, type 2 diabetes. Further laboratory investigations should be directed by the history. Measurement of plasma renin and aldosterone may help distinguish between the different causes of hypoaldosteronism but they are not always easy to interpret, especially as hyperkalaemia itself stimulates aldosterone secretion and suppresses plasma renin activity. Therefore, measurement should follow normalisation of $[K^+]$.

Measurement of transtubular potassium gradient (TTKG) can be used to evaluate the adequacy of the renal response to hyperkalaemia. It is only valid when urine osmolality is >300 mmol/kg and urine sodium is >25 mmol/L. It is calculated as:

$([Osm]_{serum} \times [K^+]_{urine}) / ([Osm]_{urine} \times [K^+]_{serum})$

TTKG is expected to be high (>10) when renal response is intact. A low TTKG in the presence of hyperkalaemia suggests hypoaldosteronism or a renal tubular defect. It is most useful in distinguishing between mineralocorticoid deficiency and resistance; following administration of fludrocortisone, TTKG will increase in mineralocorticoid-deficiency but not aldosterone-resistant states.

7.2 Low values

7.2.1 Causes

1. Spurious
   - Storage of unseparated samples above room temperature
   - Leukocytosis.
2. Inadequate intake (uncommon)
   - Anorexia nervosa
   - Severe malnourishment.
3. Intracellular uptake
   - Drugs
     - β2-agonists e.g. bronchodilators, decongestants, adrenaline, tocolytic agents
     - xanthines e.g.theophylline, caffeine
     - insulin (in overdose or in treatment of diabetic ketoacidosis)
     - verapamil (intoxication)
     - chloroquine (intoxication)
   - Hyperthyroid periodic paralysis ((hypokalaemia occurs during an attack)
   - Familial hypokalaemic periodic paralysis
   - Phaeochromocytoma.
   - Delirium tremens (β-adrenergic stimulation)

- Treatment of severe pernicious anaemia with vitamin B12.

4. Increased renal potassium excretion
   - Drugs
     - diuretics
     - mineralocorticoids e.g. fludrocortisone.
     - glucocorticoids with weak mineralocorticoid activity e.g. prednisone, hydrocortisone.
     - 11-βhydroxysteroid dehydrogenase inhibitors e.g. carbenoxolone.
     - penicillins in large IV doses
     - drugs causing magnesium depletion and therefore secondary potassium wasting e.g. aminoglycosides, cisplatin, amphotericin B.
   - Magnesium depletion
   - Diabetic ketoacidosis and hyperosmolar hyperglycaemic state (total body potassium is depleted, particularly in DKA – plasma concentrations may be normal or high)
   - Leukaemias (acute; cause unknown)
   - Chloride depletion
     - vomiting
     - nasogastric tube drainage
   - Mineralocorticoid excess
     - primary hyperaldosteronism
     - congenital adrenal hyperplasia (11β-hydroxylase and 17α-hydroxylase deficiency)
     - Cushing's syndrome and disease
     - glucocorticoid responsive aldosteronism
     - renin-secreting tumours
     - ectopic corticotropin syndrome
     - renovascular hypertension
     - malignant hypertension
     - renal vasculitis
   - Apparent mineralocorticoid excess
     - Liddle's syndrome
     - 11β-hydroxysteroid dehydrogenase deficiency
     - Liquorice (11β-hydroxysteroid dehydrogenase inhibition)
   - Impaired chloride-associated sodium transport
     - Bartter's syndrome
     - Gitelman's syndrome
   - Renal tubular acidosis
     - type I (hypokalaemia cardinal feature)
     - type II (occasional hypokalaemia).
5. Increased potassium loss in the stool
   - Drugs causing faecal potassium loss
     - laxatives
     - enemas
   - Infectious diarrhoea
   - Tumours
   - Malabsorption
   - Short bowel syndrome
   - Enteric fistula.

7.2.2 Investigation of low values

Spurious hypokalaemia must be excluded. If leukocytosis is present a lithium heparin sample, should be requested and sent immediately to laboratory.

In true hypokalaemia, review of the medical history and drug history may elucidate the cause and guide further investigation. Diuretics are one of the commonest causes. Serum bicarbonate or acid-base status should be assessed and serum magnesium should be measured.

To help differentiate renal from extrarenal causes, urine potassium should be measured. In the presence of hypokalaemia, a 24 hour urine potassium <25 mmol, or a random urine potassium <20 mmol/L (or 2 mmol/mmol of creatinine) provide strong evidence of extrarenal loss. In hypokalaemia with metabolic alkalosis, a random urine chloride <20 mmol/L indicates renal chloride retention, which suggests chloride depletion e.g. chronic vomiting. A random urine chloride >20 mmol/L (or 2 mmol/mmol creatinine) can be seen in Bartter's and Gitelman's syndrome. The effect of diuretic use on urinary chloride levels depends on the relationship of the time of urine collection to diuretic effect: it is high while the diuretic is acting, but drops to low levels afterwards. N.B. In the presence of polyuria, urinary electrolyte concentrations should be expressed in relation to creatinine concentration.

7.3 Notes

1. A $[K^+]$ >6.5 mmol/L will generally require urgent treatment, as will patients with hyperkalaemia and characteristic ECG changes. The rate of increase is also important: acute hyperkalaemia is more dangerous than chronic. The danger is ventricular fibrillation. Cacium gluconate should be given to protect the heart. The hyperkalaemia can then be corrected using 50% dextrose with a fast-acting insulin. Local protocols should be in place to guide management.
2. A $[K^+]$ <2.5 mmol/L will generally require urgent treatment, as will patients with hypokalaemia and characteristic ECG changes. Clinicians should also identify patients at risk of serious consequences of hypokalaemia i.e. the elderly, patients with arrythmogenic heart disease and patients taking digoxin. The rate of decrease is also important: acute hypokalaemia is more dangerous than chronic. IV potassium should be given cautiously: usually not more than 20 mmol/h, and not more concentrated than 40 mmol/L. Potassium should not be given if the patient is oliguric.
3. Local policies should exist for telephoning abnormal potassium results to primary and secondary care. Typical critical limits for telephoning are values of <2.5 and >6.5 mmol/l.

8 Performance

8.1 Sensitivity, specificity etc.

Hypokalaemia and hyperkalaemia are diagnosed on the basis of $[K^+]$ measurements. Sensitivity and specificity are thus 100%. Potassium measurements are not used on their own for the diagnosis of other conditions.

9 Systematic reviews and guidelines

9.1 Systematic reviews

None identified

9.2 Guidelines
http://app.mapofmedicine.com/mom/204/index.html
Hyperkalaemia
Hypokalaemia (accessed 6.vii.2012)

9.3 Recommendations
Quality of diagnostic samples. Recommendations of the working group on preanalytical quality of the German Society for Clinical Chemistry and laboratory medicine. http://www.diagnosticsample.com/ Accessed 07ii.2012

10. Links

10.1 Related analytes: none

10.2 Related tests: serum creatinine, bicarbonate (or formal assessment of acid-base status), magnesium (see 7.1.2 and 7.2.2)

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