Best practice in primary care pathology: review 9

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This ninth best-practice review examines two series of common primary care questions in laboratory medicine: (i) potassium abnormalities and (ii) venous leg ulcer microbiology. The review is presented in question-and-answer format, referenced for each question series. The recommendations represent a précis of guidance found using a standardised literature search of national and international guidance notes, consensus statements, health policy documents and evidence-based medicine reviews, supplemented by MEDLINE EMBASE searches to identify relevant primary research documents. They are not standards but form a guide to be set in the clinical context. Most are consensus rather than evidence-based. They will be updated periodically to take account of new information.

INTRODUCTION

This is the ninth in a planned series of reviews to answer a number of questions that arise in primary care use of pathology.

Each subject is introduced with a brief summary of the type of information found and is handled separately with its own reference list.

Although the individual subjects are not related, as they cover the disciplines of clinical biochemistry, microbiology, immunology, haematology and cellular pathology, they are designed (once completed) to form a resource that will be indexed and cover a wide range of the most common primary care laboratory issues, to be made available to users.

Where the new United Kingdom General Medical Services (GMS) contracts make specific reference to a laboratory test, the indicator or target is appended at the end of the answer.

HYPOKALAEMIA AND HYPERKALAEMIA (AT AND WSAS)

Out-of-range potassium results—particularly hyperkalaemia—pose a major problem in primary care, notably due to sample conditions producing spurious results.

Severe hypokalaemia or hyperkalaemia are life-threatening and require urgent attention. Distinguishing spurious from true abnormalities is therefore critical.

Much of the observational work dates back 50 or more years, but the problem of sample deterioration in primary care remains. Further work in this area appears essential to reduce the wasted resources in investigating spurious results and reducing the risk of failing to identify true clinical

emergencies. Much evidence-based research regarding prognosis for a given potassium level does not extend beyond expert opinion. It is unlikely that absolute values alone dictate risk as predisposition to arrhythmia, rate of fall and other co-existent metabolic abnormalities are likely to be of equal importance.

It is, however, important to note that prevention of hyperkalaemia is possible in many situations and certain predictive factors can be used to determine which patients to test, and how often, assisted by other results obtained from the renal and electrolyte profile.

What should I do about high serum potassium?

Identify patients at risk of having true rather than spurious hyperkalaemia or at risk from its effects

- Those with known chronic kidney disease (CKD)
- Patients on potassium-raising drugs—notably, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, potassium-sparing diuretics, potassium salts (including LO salt®) or laxatives (Movicol, Kleenprep Fybogel)
- Patients with obstructive uropathy
- Patients with clinical features such as myopathy, paralysis, arrhythmias, bradycardia
- Those at greater risk from severe hyperkalaemia: elderly (>70 years), serum urea (>8.9 mmol/l)
- Patients with acute illness (eg acute renal failure, ketoacidosis)
- Consider spurious hyperkalaemia in the absence of all the above.

Assess urgency criteria

- Severity: mild: 5.5–5.9 mmol/l, moderate: 6–6.9 mmol/l, severe: ≥7.0 mmol/l
- Changes in serum K, serum creatinine (and estimated glomerular filtration rate (eGFR) if renal function is not changing acutely). Statistically significant changes are 0.5 mmol/l, 15% and 10%, respectively. Smaller rises could reflect statistical variation
- Clinical and electrocardiogram (ECG) (K>6.0 and higher than previous sample) findings
- Values rising over 6–12 hours by >0.5 mmol/l are high risk at any K level.

Abbreviations: ACTH, adrenocorticotrophic hormone; CKD, chronic kidney disease; ECG, electrocardiogram; eGFR, estimated glomerular filtration rate; GMS, General Medical Services; HTA, Health Technology Agency

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Follow assessment and action guidance below

- Serum K ≥ 7.0 mmol/l in any patient
 - Perform ECG
 - Admit to hospital
 - Consider administering first-aid therapy, depending on urgency
- $6.0 < \text{serum K} < 7.0$ and
 - Symptoms and signs or abnormal ECG, and those receiving potassium-active agent, or
 - Significant deterioration in renal function/rise in K ($\Delta \text{K} > 0.4$ mmol/l, or $\Delta \text{creatinine} > 15\%$ / $\text{eGFR} > 10\%$)
- Perform ECG
- Review Na, bicarbonate (HCO_3), urea and creatinine levels
- Seek urgent opinion or admit to hospital, depending on urgency factors
- Stop the administration of potassium-raising and nephrotoxic drugs where possible
- $6.0 < \text{serum K} < 7.0$ and
 - Non-CKD, no symptoms and signs or abnormal ECG, and not receiving potassium-active agents
- Exclude spurious hyperkalaemia
- Seek urgent opinion
 - CKD
- K and renal function stable (eg $\Delta \text{K} < 0.5$ mmol/l, or $\Delta \text{creatinine} < 15\%$ / $\text{eGFR} < 10\%$)
- Consider ECG unless there is a chronic stable result
- Review Na, HCO_3 , urea and creatinine levels
- Establish thresholds for future action
- Avoid potassium-raising drugs
- Advise to follow potassium-reduced diet
- $5.5 \leq \text{serum K} < 6.0$
- K and renal function stable ($\Delta \text{K} < 0.5$ mmol/l, or $\Delta \text{creatinine} < 15\%$ / $\text{eGFR} < 10\%$) since the last assessment
- Review Na, HCO_3 , urea and creatinine levels
- Review possible dietary and drug influences
- Increase monitoring according to relevant guidance
- $\text{K}^+ > 5.0$ mmol/l
 - Review Na, HCO_3 , urea and creatinine levels
- No action normally required unless recent significant change ($\Delta \text{K} > 0.4$ mmol/l, or $\Delta \text{creatinine} > 15\%$ / $\text{eGFR} > 10\%$)
- Treatment with any medication that may increase the serum potassium should normally only be initiated with specialist advice.

The Joint Renal Association/Royal College Specialty Committee on Renal Disease Guidelines on chronic kidney disease guidelines (<http://www.renal.org/CKDguide/full/UKCKDfull.pdf>) define a significant deterioration in kidney disease as a fall in $\text{eGFR} > 2$ ml/min in 6 months and recommend action thresholds of a creatinine rise $> 20\%$ or a eGFR fall $> 15\%$ for increased monitoring after initiation of an angiotensin-converting inhibitor. We have adopted the figures recommended (15% and 10%, respectively) on the basis of analytical imprecision to reconcile these recommendations. Our values are dependent on the assumption that a significant change in

serum creatinine within the normal range between consecutive measurements, taking account of analytical and biological variation, is approximately 15 mmol/l (approximately 15%).

What is a high serum potassium?

The upper limit of the reference range for potassium in healthy adults is approximately 4.9–5.1 mmol/l^{1–5} in serum and 4.4–4.5 mmol/l in plasma.^{4,5} Male/female and pregnancy-related differences are probably too small to be of clinical relevance. Due to analytical and biological sample variation, a change of 0.5 mmol/l may be taken as highly likely to represent true change, with lesser differences increasingly likely to represent statistical variation.⁶

The higher values in serum occur due to the addition of potassium released from platelets on coagulation. The use of a single significant figure of 5 mmol/l has been advocated as an upper limit for serum.⁷

Hyperkalaemia can be defined simply as a serum potassium level above the population reference range, although action limits may be more appropriate. CREST[®] was the only reference found to stratify hyperkalaemia into mild, moderate and severe—mild: 5.5–6; moderate: 6.1–6.9; severe: > 7.0 mmol/l—and the EBM guidelines² define 7.5 mmol/l as the threshold for immediate first aid.

However, although action limits can be stated, the rate of increase of serum potassium is also frequently cited as a determinant of risk even if the first value is within the reference range.

Hyperkalaemia in CKD may be precipitated by small changes in diet, therapeutic drugs, changes in eGFR , new infection or new acidosis diabetic ketoacidosis. Use of LO salt[®]-type salt substitutes has also been implicated in life-threatening hyperkalaemia in renal failure.⁹ Milk, coffee and nuts are additional examples of high potassium sources. The major risk is that of arrhythmia, although symptoms of weakness, paralysis or paraesthesiae may occur.

Angiotensin-converting enzyme inhibitors and other potassium-raising drugs are common causes of hyperkalaemia. Of 1818 patients on ACE inhibitors in one study, 11% had serum potassium values greater than 5 mmol/l and 1% had severe hyperkalaemia (> 7.0 mmol/l).¹⁰

Hyperkalaemia in diabetes occurs acutely in diabetic ketoacidosis with concomitant total body depletion, or in older patients with renal impairment, hyporeninaemia or CKD, particularly diabetic nephropathy. Risk is enhanced in those over 70 years of age, in those whose serum urea exceeds 8.9 mmol/l¹⁰ and by hypoxia.⁸

A list of more common agents responsible for raising potassium are shown in table 1.

Transient hyperkalaemia

Hyperkalaemia may be transient and not common in some patients. A risk of arrhythmia is present, but this is not well defined. Vigorous exercise, such as gymnastic activities or running, increases serum potassium and should be avoided in

Table 1 Common potassium-raising agents

Name of agent
Spironolactone
Amiloride
Triamterene
Potassium salts, including salt substitutes (LO Salt [®])
ACE inhibitors/angiotensin receptor blockers
Non-steroidal anti-inflammatory agents
Transient: nicorandil Cyclosporin A

the hours before sampling. Ten minutes of vigorous exercise increases the serum potassium by up to 50% due to leakage from red blood cells and muscle cells. This effect is enhanced by B-blockers.¹¹

Performing electrocardiograms

No clear recommended thresholds for performing an ECG were found. As ECG changes are infrequently seen below 6.0 mmol/l, this would seem to be a logical threshold, although additional factors—such as previous results, rate of rise and urgency factors—are important. Lower thresholds should be considered in acute situations, when the rate of rise may be more important than absolute values.

When to admit to hospital for immediate action or institute first aid

True severe hyperkalaemia is a medical emergency, which carries a risk of potentially fatal ventricular arrhythmias as a result of nerve and muscle depolarization. Various thresholds are found in medicine textbooks, depending on the context and action recommended. Two textbooks cite a serum potassium of more than 7.0 mmol/l as a medical emergency.^{12 13} These are consistent with the CREST definition of severe hyperkalaemia.⁸ Other guidance for immediate first-aid action, however, range from 6.0 mmol/l¹ to 7.5 mmol/l,² probably reflecting the heterogeneity of clinical situations and the need to avoid excessively fixed thresholds for action.

The relationship between ECG and serum potassium and with prognosis

The sequence of ECG changes is more apparent than the relationship with the absolute serum potassium at any stage. This may reflect differences in presentation—that is, acute versus subacute versus chronic and, for example, the co-existence of hypocalcaemia. Levels at which early ECG changes occur are more variable than later changes.¹⁴ However, high T waves, the first typical changes, are not specific and can be seen in “normal” people.¹⁴ The same changes occur in hypermagnesaemia, which may account for a lack of correlation with serum potassium. CREST¹⁰ emphasizes that the decision to treat severe hyperkalaemia should not be deferred on the basis of a normal ECG. Typical ECG progression in hyperkalaemia is shown in table 2.

How should I treat severely increased or rapidly rising potassium levels?

We recommend:

- First aid will usually be carried out in secondary care
- First aid should be considered in primary care in emergency situations or when patient transfer delays are likely (eg geographical isolation); notably associated with advanced ECG changes
- Standard management is 10 ml of 10% calcium gluconate intravenously and 20 mg frusemide.

Table 2 Typical ECG progression in hyperkalaemia

Description of activity

- High-amplitude T wave (higher than R)
- Prolonged PR interval
- Reduced or absent P waves
- Peaking of T waves
- AV block
- QRS widening
- Sine wave—arrest imminent

Intravenous salbutamol (0.5 mg) has also been advocated.⁸ Although some guidance supports the conventional role of bicarbonate,² CREST recommend that risks outweigh any benefit.⁸

What should I do if I suspect a high potassium result is spurious?

We recommend:

- Considering artefactual causes if the patient has normal renal indices and serum bicarbonate, notably serum creatinine <100 micromol/l or eGFR >60 ml/min⁻¹ and none of the factors listed above are present.

Consider the following causes:

- The specimen was refrigerated or exposed to cold in transit
- Long delay between venepuncture and separation
- Difficult venepuncture with prolonged tourniquet time
- In vitro haemolysis: shaking sample, transferring to tube through a needle
- Patients with raised blood cell count (white blood cell count > 15 × 10⁹/l; platelets > 700 × 10⁹/l)
- Contamination from potassium EDTA (blood count tube anticoagulant).

Take the following action:

- Take a second specimen to arrive within 3 hours of venepuncture
- Remove the tourniquet before drawing blood
- Do not allow the specimen to cool below room temperature
- Send a simultaneous heparin specimen for potassium analysis
- If recent blood count not available, send full blood count
- If sequential samples are haemolysed, consider intravascular haemolysis.

The incidence of true clinical hyperkalaemia with “normal” urea and creatinine is described as insignificant,⁹ but should be considered before assuming a result to be spurious.

It may occur after an overdose of potassium salts or with potassium-sparing diuretics in association with normal renal function (eGFR >90 ml/min).

Causes of spurious hyperkalaemia

The main causes of spurious hyperkalaemia in primary care relate to time and temperature problems associated with transporting samples from primary care to laboratories and are exacerbated by cold and separation delays. Delays in transport can be partially addressed by ensuring adequate storage conditions. The use of centrifugation on the primary care site could resolve several of these problems, but raises practical and health and safety difficulties for the surgery.

Related to Venepuncture

Hyperkalaemia and prolonged tourniquet time

Stasis at venepuncture increases potassium concentrations in serum because of the release of potassium-rich fluid from red blood cells and muscle cells with haemoconcentration.^{15 16} Extreme stasis of 3 minutes’ duration increases the serum potassium by 10–20%. Fist clenching to localize veins can also increase serum potassium. Some guidelines recommend that specimens for electrolytes be taken first when multiple tubes are required at venepuncture to minimize the effect of stasis.

Haemolysis during blood sampling

Red blood cells contain approximately 100 mmol/l potassium. Venepuncture may cause haemolysis, which may not be visible but can be detected spectroscopically. In vitro, this is a function of the storage time and exposure to cold temperatures. Mechanical damage to red blood cells occurs due to cavitation when expelling blood through fine-bore needles¹⁷ or during difficult venepuncture with excessive pressure applied to a syringe. Shaking specimens either to mix with anticoagulant or accidentally results in mechanical haemolysis. This may increase the potassium concentration four-fold.¹⁸

More potassium is released when red blood cells leak haemoglobin to produce visible haemolysis. Serum haemoglobin levels of 0.5 g/l increases a serum potassium of 5 mmol/l by 10%,¹⁷ although the effect is variable between specimens. Visible haemolysis invalidates serum potassium results.¹⁹

In vitro haemolysis is also more likely in patients with a family history of haemolytic disorder.²⁰

A correction has been proposed using a measure of the degree of haemolysis, interpreted qualitatively on the report form as normal, critically high or critically low,²¹ although this is not routinely used.

Related to sample storage

Refrigeration of samples

Failure of the Na-K-ATPase in the cell membrane will increase the serum potassium, whether this occurs in vitro or in vivo. In vitro, cold reduces Na-K-ATPase activity. Trull *et al.*²² undertook a study confirming old data suggesting that refrigeration of specimens increased serum potassium values and reported that storage of specimens above 20.3 °C minimized this effect. Using insulated boxes for transport was suggested to avoid erroneous results.

One report, not described in detail, describes issuing simple guidance to users on needle size (21 gauge) and storage at room temperature, which reduced the proportion of samples with serum potassium >5.0 mmol/l almost exclusively to those that had been left overnight before being centrifuged. This report was based on a laboratory where most samples arrived within 4 hours after being taken from the patient.²³

Potassium has also been reported to be stable in whole blood for 16 h at 18 °C,²⁴ suggesting that further work to provide a systematic answer to the practical aspects of sample storage and delivery could potentially reduce this common primary care problem.

High cell counts: pseudohyperkalaemia

Potassium is released from platelets during blood coagulation. Platelet counts of more than $1,000 \times 10^9/l$ will affect the serum potassium noticeably.²⁵ It has been estimated that a $100 \times 10^9/l$ increase in platelets increases the serum potassium by 0.15 mmol/l.²⁶ Heparinised plasma is not subject to this release and will therefore have a more reliable potassium level. The difference between serum and plasma potassium may be more than 1.0 mmol/l in thrombocytosis.²⁷

Severe leucocytosis (more than $20 \times 10^9/l$) can result in excess potassium leakage.¹⁸ This applies particularly when samples have been stored in the cold for reasons explained above. It is exaggerated in leukaemic cells, which are more leaky. Conversely, with storage at room temperature, leucocytosis may result in potassium uptake that is sufficient to make a result from a hyperkalaemic patient appear normokalaemic (or even hypokalaemic).²⁸ Plasma potassium may still be elevated spuriously with leucocytosis but less so than serum, and it is advisable to have these specimens separated rapidly and kept at room temperature until analysis.

Similar changes may occur with hereditary or acquired stomatocytosis, and other red blood cell disorders, which

exaggerate the potassium release during prolonged storage and may require rapid separation within 1 hour,²³ implying that venepuncture occurs close to the site of analysis.

In vivo haemolysis

Finally, in addition to exaggerating potassium release on storage, congenital or acquired haemolytic diseases, embolism and extensive tissue breakdown (such as the tumour lysis syndrome) will also promote in vivo potassium release.

It is important to note that this represents true hyperkalaemia and treatment is directed towards that of the underlying condition and occasionally of the hyperkalaemia itself, which can be life-threatening.²⁹

The main diagnostic problem with intravascular haemolysis is that the serum potassium result is not reported by laboratories when visible haemolysis is present.¹⁹ This policy is appropriate for in vitro haemolysis but raises problems with in vivo haemolysis. Laboratories should be contacted specifically to discuss cases of hyperkalaemia that are suspected to be associated with in vivo haemolysis.

GMS contract indicator: None.

What should I do about low serum potassium levels?

Identify patients at risk of hypokalaemia or from its effects

- Existence of risk factors: elderly, arrhythmogenic heart disease
- Definitions of mild, moderate and severe may not be applicable in these patients—any level of hypokalaemia may have serious potential consequences.

Assess urgency criteria

- Severity: mild: 3.1–3.5; moderate: 2.6–3.0; severe: ≤ 2.5 mmol/l
- Rate of change/magnitude of change since last sample
- Falls are of increasing significance as they approach 0.5 mmol/l
- Smaller changes may reflect statistical variation.

Consider action guidance below

- Serum K < 2.6 mmol/l in any patient:
 - Compare with previous result
 - Repeat test on emergency basis if inconsistent with previous result
 - Seek urgent specialist advice
 - Perform ECG
 - Admission normally indicated
 - Consider administering first aid if a critical ECG emerges.
- Serum K > 2.5 < 3.0 mmol/l in any patient:
 - Compare with previous result
 - Repeat test on same/next-day basis if inconsistent with previous result
 - Assess symptoms signs and risk status
 - Perform ECG
 - Seek urgent specialist advice if symptoms or at-risk patients
 - Weigh risks and benefits of ambulatory potassium replacement on individual case basis.
- 3.1 < Serum K < 3.5:

- Compare with previous result—may be transient
- Repeat test, adding creatinine, sodium and bicarbonate
- Values of 3.3–3.4 mmol/l in otherwise untreated low-risk individuals may be of limited clinical significance
- Ambulatory replacement reasonable if indicated.

How should I investigate low serum potassium levels?

If the cause is obvious:

- Investigate and treat any underlying cause such as diarrhoea
- Treat or replace according to cause

If the cause is unclear:

- Review medication list for other drugs known to cause hypokalaemia
- Consider nutritional status and dietary intake
- Consider sending a random urine test for K:creatinine ratio or 24-hour urinary potassium to identify renal loss
- Consider possibility of sample being stored in a warm environment before being separated (pseudohypokalaemia). Repeat if suspected; sample ideally being taken at hospital
- If hypertensive, consider need for renin-aldosterone studies
- Consider ectopic adrenocorticotrophic hormone (ACTH) production, particularly if severe or rapidly falling.

How should I treat low serum potassium levels?

Oral ambulatory treatment (mild hyperkalaemia and low-risk moderate hypokalaemia)

- Treatment of the underlying cause
- Dietary supplementation
- Potassium supplementation (40–120 mmol/day depending on deficiency and urgency)
- Regular potassium monitoring, weekly to several times weekly depending on deficiency
- Target concentrations of up to 4.5 mmol/l and above may be appropriate in higher-risk patients.

High-risk, moderate and severe hypokalaemia

- Seek secondary care advice for consideration of intravenous replacement.

What is a low serum potassium level?

Reports of the lower limit for potassium levels vary slightly between 3.5 mmol/l⁵ and 3.3 mmol/l in serum and plasma, respectively;³⁰ in plasma, it has been reported to be 3.4 mmol/l in women and 3.5 mmol/l in men.⁵ The figure of 3.5 mmol/l is generally accepted for serum.

Low potassium levels can be described as mild (3.0–3.5 mmol/l)¹, severe (<3.0 mmol/l³¹ or <2.5 mmol/l)¹ and, by implication, moderate (2.5–3.0 mmol/l)¹. A further guideline defines a threshold of oral and intravenous replacement of 3.0 mmol/l.³²

The definitions of <3.5, <3.0 and <2.5 mmol/l as mild, moderate and severe, respectively, appears practical, but we believe that they should be applied only in patients with no risk factors for arrhythmia. As discussed below, different risk thresholds are reported in at-risk patients and, in the classical risk situation of acute myocardial infarction patients with potassium concentrations below 4.0 mmol/l, were reported to be at significantly increased risk of ventricular arrhythmias.³³ Mild and moderate hypokalaemia of 2.5–3.5 mmol/l, and potassium concentrations in the lower part of the reference

range, should therefore be considered to have severe potential impact in the at-risk patients.

Muscle necrosis is said to occur at levels less than 2.5 mmol/l, but a primary reference has not been found to substantiate a definite value.

Values below the normal range are defined as hypokalaemic, although several observational studies have reported adverse outcomes in at-risk people with serum potassium concentrations at a higher threshold (3.7 mmol/l) (patients receiving digoxin³² and recommended potassium supplementation to maintain serum potassium concentrations at 4.0 mmol/l³⁴ and 4.5–5 mmol/l³⁵ in higher-risk patients). This area would benefit from further guidance.

At-risk patients have included: patients receiving digoxin and patients with cardiac disease (ischaemia, failure or left-ventricular hypertrophy).

Hypokalaemia is not, however, synonymous with whole-body potassium depletion^{1 34} and may be associated with primary alkalosis or redistribution.

Conversely, in whole-body potassium depletion, serum potassium values may be normal and associated with alkalosis, which may be the only evidence of potassium depletion. The serum bicarbonate is therefore a useful additional investigation.

The major risk is that of arrhythmia. A list of classical signs, symptoms and findings is shown in table 3.

Mechanism of hypokalaemia

Depletional hypokalaemia

Renal losses

The most common cause of hypokalaemia in primary care is diuretic use (loop or thiazide), which is less common in otherwise healthy people than in those with predisposing disease such as heart and liver disease.³⁴ The next most common cause is hyperaldosteronism, which occurs due to heart failure or liver disease. In most of these situations, the underlying disease and drugs involved may be clinically obvious.

Additional common causes of renal depletion are those of secondary hyperaldosteronism. Rarer causes include the renal Liddle's and Bartter's syndromes and renal tubular acidosis (types 1 and 2).

When the cause of hypokalaemia is unclear, a urinary potassium measurement will help to identify renal loss. The agreed 'reference' method for this is 24-hour potassium excretion, although as this is often impractical and inaccurate in primary care, alternatives are proposed. Such alternatives include the potassium:creatinine ratio³⁶ and more complex calculations (also reviewed in³⁶), which are less likely to be used in primary care.

Urine potassium excretion of less than 15–20 mmol/24 hours¹ are reported to indicate non-renal losses, and greater than 20–25 mmol/L to suggest renal loss. This is approximately equivalent to a potassium:creatinine ratio >2.5 in a person of

Table 3 Symptoms and signs of hypokalaemia

Symptoms

Arrhythmia, ECG changes (ST depression/T-wave flattening or inversion/U waves)
Digoxin sensitivity
Muscle weakness/rhabdomyolysis
Lethargy/confusion
Tetany: extensor muscle spasms of hands and feet
Paraesthesiae of hands and feet
Flaccid paralysis
Polyuria/renal tubular dysfunction
Ileus/reduced GI motility

average body mass, which was validated in one study of hypokalaemic periodic paralysis and non-hyperkalaemic paralysis.³⁶

High normal serum sodium and normo- or hypokalaemia are typically seen in primary hyperaldosteronism (Conn's syndrome), which should be considered in patients with refractory hypertension. Laboratories vary in the tests available for investigation of the renin-angiotensin-aldosterone axis, and local specialist advice is recommended for the rare suspected cases of Conn's, Bartter's, Liddle's, liquorice overuse and other potassium-wasting syndromes. Abuse of diuretics or alkalis such as Milk of Magnesia® should be considered among the rarer causes. Ectopic production of ACTH may cause rapid onset and severe hypokalaemia.

Extra-renal depletion

With extra-renal depletion of more than 5 days' duration, the healthy kidney conserves potassium and urinary output is typically less than 15–20 mmol/24 hours.^{1 31} Random urine concentrations can be misleading because of the induced polyuria. Causes include inadequate ingestion due to fasting or the "tea and toast diet" in the elderly.

Losses from the lower gastro-intestinal tract are common causes, which are usually associated with hyperchloraemic acidosis due to bicarbonate loss. Causes to consider include laxative abuse, villous adenomas, secretory small-bowel diarrhoea and inflammatory bowel disease. Vomiting produces hypokalaemia if prolonged, or in infants or frail elderly patients as a result of alkalosis. Most of these causes should be clinically apparent.

Redistributional hypokalaemia

Redistribution from the extracellular to the intracellular compartment may occur acutely in alkalosis, as a result of administration of insulin in ketoacidosis, and in the rare situation of familial and sporadic hypokalaemic periodic paralysis, although these would normally represent secondary care situations.

A combination of depletion and redistribution can occur in catecholamine release or administration of beta-mimetics (a nebulised dose of inhaled beta mimetic may reduce potassium by 0.2–0.4 mmol/l and a second dose shortly after by 1 mmol/l).³⁴

Redistribution also occurs in re-feeding after starvation, in stress due to surgery or severe illness, and in the acute treatment of pernicious anaemia.

Redistributional hypokalaemia is not a common scenario in non-acute presentations.

Pseudohypokalaemia

Storage of unseparated blood at high ambient temperatures, such as during hot weather, may result in spurious hypokalaemia. Masters *et al.*³⁷ reported no reduction after 4 hours at 23 °C, a fall of 0.2 mmol/l in 4 hours at 37 °C; another report described a fall of 0.22 mmol/l after 2 hours at 25 °C.²⁴

This is more pronounced when the white blood cell count is raised²⁸ and may produce apparent hypokalaemia in a normokalaemic patient. Time and temperature effects are, however, complex. The effects of temperature on lowering serum potassium seem to be quantitatively far less than those such as storage of unseparated blood overnight or at low temperatures, which increase it. However, this effect may make a result appear slightly lower than it actually is. The lowering effect may be greater in plasma than in serum.³⁸

ECG abnormalities

Hyperpolarisation of the excitable membranes occurs in hypokalaemia. This increases the threshold for initiation of an action potential and interferes with its termination.

Apart from arrhythmia, ECG findings are reported to appear with increasing frequency and severity at serum concentrations of 3.0 mmol/l and below.^{1 32}

No thresholds for performing ECGs are reported. In the absence of these, we have recommended indicative thresholds of 3 mmol/l as the threshold between 'mild' and 'moderate' hypokalaemia, and the threshold at which ECG abnormalities are commonly seen.³² The severe impact of mild hypokalaemia in at-risk people would, however, justify a higher threshold for considering ECG in this group—particularly if the hypokalaemia is of rapid onset.

Hypomagnesaemia

Gastro-intestinal potassium losses and diuretic-induced hypokalaemia both commonly co-exist with hypomagnesaemia,^{1 39} which may predispose to or aggravate arrhythmias and render potassium-replacement ineffective. Although we found no clear guidance on magnesium replacement, we recommend that magnesium measurement be considered at least in patients with severe or refractory hypokalaemia and those with serious arrhythmias, although the latter are more likely to reflect a secondary care patient group.

Potassium replacement

Oral replacement is preferred,^{31 32} using potassium-rich foods and supplementation. Dietary sources of potassium include: coffee, nuts, fruits, tomatoes, bananas and chocolate. Tomato juice contains approximately 8 mmol per standard 100 ml glass.

Of the different formulations, wax matrix-based formulations (such as Slow-K®) have been associated with cases of gastric erosions in some people.³⁴ In the UK, the British National Formulary (BNF) recommends liquid-based or effervescent preparations as first line,⁴⁰ although liquid potassium chloride is reported as being less well tolerated by others and tablet formulations have been recommended,³⁴ partly for compliance reasons.⁴¹ Effervescent tablet preparations, if well tolerated, would appear a priori to represent a compromise between rapidity of action, dosage convenience and gastric safety.

Potassium deficiency can be estimated from the serum concentration in depletion states: approximately 100 mmol per 0.3 mmol/l below "normal" for the patient,^{1 31 42 43} with proportionately greater deficit when serum potassium is below 2.5 mmol/l.³¹ Doses of 40–120 mmol per day¹ may be required for replacement, depending on the deficiency and urgency of replacement; 20–40 mmol/l may be required for prevention.

In the UK, potassium-sparing diuretics are recommended as the preference for patients on potassium-lowering diuretics.⁴⁰ One review of randomised trials⁴⁴ found a doubling in mortality rate in patients receiving thiazide versus potassium-sparing diuretics, and several authors recommend routine potassium supplementation or potassium-sparing agents in patients receiving diuretics.^{34 35 44}

A list of more common drug-induced causes of hypokalaemia is shown in table 4.

Inpatient intravenous treatment (moderate symptomatic and at-risk patients and severe hypokalaemia)

Treatment of severe depletion is normally carried out in hospital as intravenous treatment is hazardous and impractical in most ambulatory situations.

GMS Contract indicator: None.

INVESTIGATION OF VENOUS LEG ULCERS (RH-J AND CAMM)

These questions and answers make recommendations about infection diagnosis and the use of microbiology services in the

treatment of venous leg ulcers in primary care. This guidance is based on evidence discussed in detail in Health Protection Agency and PRODIGY guidelines and other key references quoted. Although the sampling techniques are equally applicable to all leg ulcers, the management advice relates specifically to venous leg ulcers and not diabetic foot ulcers, for which specialist advice is recommended.

Venous leg ulcers affect 1.7% of those aged ≥ 65 years.⁴⁵ Compression bandaging is the recommended treatment to heal uncomplicated venous leg ulcers.^{46–49} All venous leg ulcers contain bacteria; most are colonisers, but some cause clinical infection.⁵⁰ Microbiology investigations should only be undertaken when there are clinical signs of infection.⁴⁶

What can a microbiological sample from a venous leg ulcer tell me?

- The organisms present and their antimicrobial susceptibilities only
- Microbiology swab samples cannot be used to determine the presence of infection in a leg ulcer.^{49–51}

A UK Health Technology Agency (HTA) systematic review has been conducted to look at sampling and treating infected diabetic foot ulcers (but also included studies on venous leg ulcers due to the expectation of only a limited number of relevant studies).⁵¹ This review identified one study addressing the diagnostic performance of specimen collection techniques, which suggested that wound swabs were not a useful tool for identifying infection in chronic wounds (defined as $>10^5$ colony-forming units per gram of tissue).⁵²

When should I sample a venous leg ulcer?

We recommend submitting a sample:

- When clinical criteria indicate that infection is present:^{46 47 49 51}
 - Increased pain
 - Enlarging ulcer
 - Cellulitis
 - Pyrexia.

And that

- A microbiology sample should only be taken when antimicrobials are indicated
- The sample should be taken before antibiotics are started^{47 53}
- Routine bacteriology sampling should not be undertaken.^{46 49}

The diagnostic performance of clinical examination in the identification of infection was reviewed in the HTA systematic review by Nelson *et al.*⁵¹ Only one relevant study was identified.⁵⁴ The validity of classic signs of infection (pain, erythema, oedema, heat and purulent exudate) and signs specific to secondary wounds (serous exudate plus concurrent inflammation, delayed healing, discolouration of granulation tissue, friable granulation tissue, pocketing of the wound base, foul odour and wound breakdown) were investigated. Infected ulcers were defined as those with 10^5 or greater organisms per gram of viable tissue or wounds containing β -haemolytic *Streptococcus*. Only increasing pain and wound breakdown were identified as valid predictors of infection. Purulent exudate was found to be a poor predictor of infection. This study was based on a small number of patients ($n = 36$) and included a variety of wound types, only 7 of which were venous ulcers. Its findings should therefore be treated with caution.⁵¹ Cellulitis is an acute spreading infection that extends into the subcutaneous tissue and

pyrexia is a recognised characteristic of infection, although it can be due to non-infectious causes.⁵⁵

Microbial contamination of leg ulcers is universal but is not thought to adversely affect healing. Routine bacteriology is therefore of no benefit.^{46 49} Nelson *et al.* found no trials that compared empirical antibiotic treatment with treatment following diagnostic tests.⁵¹

How should I sample a venous leg ulcer for microbiological investigation?

Tissue biopsy is the gold standard.⁵⁶ Wound swabs offer an easy-to-use and low-cost alternative.

To take a sample, we recommend:

- Use a swab with transport medium and charcoal, to aid survival of fastidious organisms^{53 57}
- Cleanse the wound with tap water or saline to remove surface contaminants⁵⁸
- Slough and necrotic tissue should also be removed^{47 56}
- Swab viable tissue displaying signs of infection whilst rotating the swab
- With all specimens, include all clinical details (about patient, ulcer and current or recent treatment) to enable accurate processing and reporting of the specimen.

Quantitative tissue biopsy is considered to be the gold standard for identifying infection and causative pathogens present in the deep tissue of wounds.⁵⁶ However, tissue biopsy is unavailable in many settings and is skill-intensive for both the laboratory and the clinician, and invasive for patients.⁵⁹ Wound swabs are suggested here as a practical alternative, although there is disagreement in the literature regarding the correlation between swabs and biopsies. There is also concern that swabs only identify surface organisms not infecting pathogens, although surface contamination can be reduced by correct wound-bed preparation.⁵⁶

The review by Fernandez *et al.*⁵⁸ refers to the use of tap water or saline for the routine cleansing of wounds. There is little evidence regarding the benefit of wound cleansing prior to sampling. However, to minimise the likelihood of obtaining only surface contaminants, wound cleansing prior to sampling is recommended.⁵⁶

There is limited evidence regarding the optimal swabbing technique to identify potentially causative pathogens. Other suggested techniques for swabbing include targeting areas of necrotic and moist tissue, taking swabs before debridement, moistening swabs prior to sampling, sampling wound exudate and swabbing the whole area of the wound using a z-shaped motion.^{59 60}

How do I interpret the laboratory report?

We recommend that interpretation be based on:

- Organisms isolated and amount of growth:
 - Group A β -haemolytic streptococci can be associated with significant infection and delays in healing^{56 61}
 - The significance of other organisms, including β -haemolytic streptococci and *Staphylococcus aureus* (including MRSA), is less clear but may be associated with infection when signs of clinical infection are present
 - Bacterial contamination of wounds is not considered to adversely affect healing^{46 61}

Antibiotic susceptibilities: The inclusion of antibiotic susceptibilities in the report does not necessarily mean that an organism is significant or that it requires antibiotic treatment.

The evidence for singling out β -haemolytic streptococci originated from work based on surgical wounds that would not heal when this organism was present.⁵⁶ Venous leg ulcers colonised with β -haemolytic streptococci have been found to heal significantly slower than ulcers with no growth or skin flora only.⁶¹ Reviews of the evidence suggest that other resident microflora of chronic wounds have little effect on healing.⁵⁶

Evidence and guidelines recommend that infection is determined by clinical criteria; however, laboratory reports that include susceptibility results frequently lead the healthcare professional to prescribe or recommend antibiotic treatment.⁶²

How do I treat a wound that is clinically infected?

- Systemic antibiotics are indicated in the presence of cellulitis or clinical infection.
- First-line treatment: Empirical therapy with oral flucloxacillin (erythromycin if penicillin-hypersensitive) 500 mg, four times a day, for 7 days. Review after 3 days in light of the microbiology results.⁴⁷
- Refer to local microbiology laboratory for MRSA treatment recommendations. MRSA colonization is not an indication for treatment, which is based on clinical criteria.
- Refer to PRODIGY guidelines for full treatment protocols: http://www.prodigy.nhs.uk/qrg/venous_leg_ulcer_infected.pdf and http://www.prodigy.nhs.uk/qrg/cellulitis_acute.pdf.

Empirical treatment with flucloxacillin is recommended for infected leg ulcers, as *Staphylococcus aureus* is the most prevalent potential pathogen.⁵⁶ There is limited evidence and a lack of consensus regarding the optimum duration of treatment for cellulitis.⁶³ Current PRODIGY guidelines recommend 14 days of treatment for infected leg ulcers; however, this is shortly to be changed to 7 days to be in line with PRODIGY's more recent guidance on the treatment of cellulitis.⁶⁴

GMS Contract indicator: None.

CONCLUSION

This ninth review brings us to a running total of approximately 105 question-and-answer sets written in order to provide an overview of current advice in use of laboratory tests in primary care. Answers to the first 8 question-and-answer sets can be found in eight previously published references.^{65–72} They have all used a common search methodology⁷³, although where recent systematic reviews have been performed, the guidance also relies heavily on the findings of these reviews. For authors wishing to consult the UK General Medical Services Contract and related quality and Outcomes framework, these can be found in previous published references.^{74–76}

Table 4 Common potassium-lowering agents

Name of agent
Diuretics: particularly loop and higher-dose thiazides, metolazone and indapamide
Mineralocorticoids
Beta-mimetics, caffeine and theophylline
Insulin
High-dose penicillin
Drugs causing hypomagnesaemia
Aminoglycosides
Cisplatin
Amphotericin B
Verapamil or chloroquine overdose
Laxative abuse
Liquorice

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