REVIEW

Best practice in primary care pathology: review 6

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This sixth best practice review examines four series of common primary care questions in laboratory medicine: (1) laboratory monitoring in hypertension and heart failure abnormalities; (2) markers of inflammatory joint disease; (3) laboratory investigation of chronic diarrhoea; and (4) mumps and chickenpox. The review is presented in question–answer format, referenced for each question series. The recommendations represent a precis 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 based rather than evidence based. They will be updated periodically to take account of new information.

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

Each topic is introduced with a brief summary of the type of information found, followed by the related questions and answers, with main recommendations listed as bullet points accompanied by a justification.

Although the individual topics 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.

In instances where the new UK General Medical Services (GMS) contracts make specific reference to a laboratory test, the indicator or target is appended at the end of the answer.

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RENAL FUNCTION AND ELECTROLYTE MONITORING IN PATIENTS RECEIVING DIURETICS, ANGIOTENSIN-CONVERTING ENZYME INHIBITORS OR ANGIOTENSIN II RECEPTOR ANTAGONISTS IN PRIMARY CARE (JJC, TMR, WSAS)

These questions cover a wide range of clinical scenarios in primary care, and are written to guide the monitoring of ambulatory patients only outside the acute setting. As the diagnoses of hypertension and heart failure group together a wide range of clinical and biochemical scenarios, it is not possible to produce guidance that covers every situation, although the published recommendations available concur on most general principles. These answers should therefore be interpreted as principles to guide monitoring in such patients.

References to nephrology advice in these answers requires further work to establish actions to take in such patients, as it is probably not practical or even desirable for all patients with raised serum creatinine (>200 μmol/l or estimated glomerular filtration rate (eGFR) <30 ml/min) to be referred to nephrology services. Further guidance needs to be developed for these situations, and the thresholds cited are intended as limits where further advice is recommended before initiating or continuing the treatments described.

Another difficulty that monitoring introduces in primary care is the production of reliable potassium results in practices served by a distant specimen collection service, when sample deterioration may adversely affect, particularly potassium, results. This is a topic that merits further examination in the context of primary care monitoring.

Drugs are treated broadly by class, which does not take account of possible intraclass specificities. In instances where reference is made to spironolactone, it would seem reasonable to extrapolate to eplerenone, pending future guidance.

Higher-risk patients include those with existing renal dysfunction(eg, stage 3 chronic kidney disease), patients aged ⩾60 years, those receiving combination therapy (eg, angiotensin-converting enzyme inhibitors (ACEI)/diuretics or potassium-sparing drugs) and those with relevant concomitant disease such as peripheral vascular disease, diabetes.

How often should renal function (creatinine, and electrolytes) be monitored in patients with heart failure receiving diuretics, ACEI or angiotensin II receptor antagonists?

We recommend:

- before initiating treatment
- 1–2 weeks after each dose increase/relevant drug addition in low-risk patients

Abbreviations: ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor antagonists; CRP, C reactive protein; eGFR, estimated glomerular filtration rate; ESR, erythrocyte sedimentation rate; FBC, full blood count; GFR, glomerular filtration rate; GMS, General Medical Services; HLA, human leucocyte antigen; RhF, rheumatoid factor; SpA, spondyloarthritides; VZIG, varicella-zoster immunoglobulin; VZV, varicella-zoster virus

- 5–7 days in higher-risk patients (eg, those receiving spironolactone, those with existing renal dysfunction, those receiving combination therapy or any of the above)
- during intercurrent illness
- remeasuring within 2 weeks if serum creatinine rises >20% or eGFR falls >15%[1]
- during chronic treatment, every 3–6 months in stable higher-risk patients up to annually in stable lower-risk patients.[1]

Many drug classes are used in the treatment of heart failure. Guidance for ACEI and angiotensin II receptor antagonists (ARBs) is given in Veterans Health Administration DoVA.[2] Glomerular filtration falls in patients receiving these drugs. In addition, hypokalaemia may occur with both thiazide and loop diuretics, and hyperkalaemia with potassium-sparing diuretics (triamterene, amiloride and spironolactone), an ACEI or ARB. Electrolytes should be measured more often if the patient is receiving both diuretics and digoxin, or if they become hypokalaemic or hyperkalaemic.[2] A compromise may be required between peripheral oedema and acceptable serum electrolyte and renal function results, with lower doses in patients with reduced glomerular filtration rate (GFR).

With potassium-sparing diuretics, notably spironolactone or eplerenone in the context of heart failure, the European Taskforce guidelines recommend that serum potassium and creatinine should be checked after 5–7 days and the dose titrated accordingly, and that values should be rechecked every 5–7 days until the potassium values are stable.[3] The Renal Association guideline[1] refers to 1–2 weeks in the context of ACEI or ARB. This patient group represents a continuum for low to higher risk depending on age, renal function and drugs used, and the retest interval reflects this within the general guideline of 5–14 days. Practitioners should be aware that because of method differences, creatinine and eGFR results from different laboratories may not be reproducible and should make themselves aware of result differences if more than one source of testing is used (eg, two laboratories or points of care testing).

This guidance refers specifically to clinically stable patients in primary care as inpatients are, by definition, potentially unstable and will usually require more frequent monitoring of renal function. It is recommended that the serum electrolytes and renal function be checked every 1–2 days, according to the diuretic response in acute circumstances[4] or if admitted to hospital.

Diuretics are often prescribed in increasing doses, and combinations of diuretic classes are also used. Combinations of thiazide and loop diuretics can cause a powerful diuresis in patients with previously diuretic-resistant oedema. Patients are often initiated on this combination treatment in hospital and will therefore have more frequent monitoring. Patients out of hospital should remain under close clinical supervision, and may receive combination treatment on a once-weekly or twice-weekly basis initially.[5] These patients are at higher risk of worsening renal function and hyponatraemia and should have their renal function checked 5–7 days after starting this combination or increasing doses within the combination treatment, and thereafter at a retest interval of 5–14 days depending on stability. Combination treatment also requires monitoring of weight and hydration status, and evidence of too rapid a diuresis or dehydration should prompt earlier testing. Most guidance refers to serum creatinine and/or eGFR as the renal indicators, although many practitioners will use serum urea as an additional indicator of hydration status.

Diuretics should be used in the lowest possible doses to control symptoms of fluid overload,[6] but patients often run into problems with deteriorating renal function or deranged electrolytes at these doses. Renal function should be checked before initiating treatment and 1–2 weeks after each dose increment.[1 3 6]

Spironolactone (low dose) has been shown in the Randomized Aldactone Evaluation Study to reduce morbidity and mortality in patients with heart failure.[7] Electrolytes should be monitored to avoid dangerous hyperkalaemia (see question below for guidance).[3] Patients shown to benefit from this treatment were those with severe heart failure (New York Heart Association classes 3 or 4) who are likely to be under hospital follow-up and/or shared care. Studies since the publication of the Randomized Aldactone Evaluation Study have shown that cohorts of patients treated with spironolactone for heart failure have shown higher rates of hyperkalaemia than those in the original trial.[8] Following the trial protocol, the monitoring of electrolytes was performed within a week of starting treatment, at 4, 8 and 12 weeks, and then every 3 months during treatment if stable. In view of more recent evidence, however, it is recommended that spironolactone (or other agents with potassium-sparing properties, eg, amiloride and triamterene) be introduced at a low dose for 1 week, with a check of serum potassium and creatinine after 5–7 days, with titration of the drug as necessary.[3] The blood tests should be rechecked every 5–7 days until the potassium values are stable.[3]

Existing guidelines concur that serum creatinine and electrolytes should be measured at 5–14 days after initiating treatment with an ACEI or ARB and 1–2 weeks after any dose increase.[1 9] Thereafter, during chronic treatment serum creatinine and electrolytes should be checked between every 3–6 months afterwards,[6] up to annually, depending on renal function.

How often should renal function tests be monitored in patients with hypertension receiving, ACEI or ARB? We recommend:

- Before initiating treatment.
- 1 week after starting treatment or any subsequent dose increase.[10]
- At 4 and 10 days after starting treatment or increase in dose in patients at higher risk of developing hyperkalaemia or deteriorating renal function (eg, peripheral vascular disease, diabetes mellitus, pre-existing renal impairment and older patients).[11]

Consider seeking further advice if a patient has:

- Renal impairment (serum creatinine >200 μmol/l or eGFR <30 ml/min) or confirmed/suspected renovascular disease before initiating ACEI/ARB.[12]
- Marked creatinine rise (⩾30%) with large fall in blood pressure after starting ACEII or ARB may suggest renovascular disease that should be investigated.[13]

The major risks of using an ACEI/ARB are of hyperkalaemia or deterioration of renal function. The general consensus is that serum creatinine and electrolytes should be measured 1 week after initiating treatment with an ACEI or ARB and 1 week after any dose increase.[10] A limited elevation in serum creatinine (ie, ⩽30% above baseline) is a common occurrence in patients after the initiation of ACEI or ARB, and if it occurs will happen within the first 2 weeks of treatment.[14] During chronic treatment, repeated measurements should be initiated only if the patient's clinical condition worsens or additional treatment is started, else it is considered best to repeat renal function and electrolytes every 3–6 months.

Patients with hypertension with raised serum creatinine (serum creatinine >200 μmol/l) before starting treatment may have renovascular disease, intrinsic renal disease or obstructive uropathy, and therefore should be referred for specialist evaluation before receiving either diuretic or ACEI or ARB treatment.[12] Referral is also recommended if the serum creatinine rises ⩾30% are associated with a large reduction in the blood pressure after initiating treatment with ACEI or ARB, as this may suggest renovascular disease.[13] Caution is required if the serum creatinine is >150 μmol/l, although in many patients with intrinsic renal impairment the creatinine will not increase further and may fall with treatment.[10]

Patients with hypertension are often treated with ACEI or ARB, but many patients are also receiving other drugs, and commonly ⩾3 agents are needed to control blood pressure. In difficult hypertension, there is an increasing vogue to use different approaches including a combination of ACEI and ARB, or the addition of spironolactone. These approaches may increase the frequency of monitoring necessary, as early and potentially more serious changes in renal function tests may occur.

How often should electrolytes/renal function tests be measured in patients with hypertension receiving diuretics?

We recommend:

Thiazide or loop diuretics

- within 4–6 weeks of starting low-dose thiazide diuretic treatment[10] or loop diuretic treatment
- thereafter, in all patients every 6–12 months[15]
- or if a person's clinical condition changes or a potentially interacting drug is added.

Spironolactone or potassium-sparing diuretics

- before initiation of treatment (it should not be initiated if the potassium values >5 mmol/l)
- after 5–7 days with dose titration if required
- every 5–7 days until the potassium values are stable
- 1–2 times/year up to every 4–8 weeks during chronic treatment, depending on risk factors (older patients, renal or cardiac dysfunction).

If potassium rises to >6 mmol/l, spironolactone or potassium-sparing diuretics should be stopped and specialist advice sought. Concomitant use of potassium sparing diuretics and ACEI or ARB should normally be reserved for practitioners experienced in such combinations and with increased monitoring as for high-risk patients.

All classes of diuretics are used to treat patients with hypertension. Thiazide diuretics (eg, bendroflumethiazide) are more likely to cause hyponatraemia compared with the other classes. This adverse effect seems to be more common in elderly people.[16] Thiazides may also cause hypokalaemia with the risk of increasing arrythmias, and it is therefore recommended that electrolytes be checked after 4–6 weeks of initiation of treatment to monitor for these effects.[10] It is logical to recheck electrolytes and renal function if a person's clinical condition changes; lethargy, dizziness or vomiting for example may indicate the development of hyponatraemia. The addition of any treatment that may potentiate the adverse metabolic effects of diuretics should also prompt rechecking of electrolytes and renal function. Thereafter, during stable chronic treatment, renal function and electrolytes should be measured every 6–12 months,[15] especially as adverse effects such as diuretic-induced hyponatraemia may be insidious and appear even after prolonged treatment.

Loop diuretics are associated with hypokalaemia and impaired renal function (via pre-renal mechanisms) because of their potent diuretic effect. Loop diuretics are used less commonly in hypertension than thiazides, and are generally reserved for patients with coexistent heart failure or renal impairment. The monitoring requirements for loop diuretics are less clear, but we believe it is reasonable to recommend the same guidance as for patients given loop diuretics for heart failure.

Aldosterone antagonists and potassium-sparing diuretics (eg, spironolactone, amiloride) are increasingly used for primary hypertension in addition to their previous use in specific causes of secondary hypertension. Use of these agents, often added to ACEI or ARB, changes the frequency of creatinine/electrolyte monitoring necessary and can cause severe hyperkalaemia. Specialist guidance should be considered before using such combinations (in our opinion). Hyperkalaemia is asymptomatic and dangerous, therefore close observation is the only way of avoiding the potential harms of treatment. Guidance on testing intervals is limited; the American Joint National Committee[17] recommends potassium measurement 1–2 times/year in all patients treated with diuretics, not separating by class. Pending more specific guidance, we therefore recommend that monitoring should range from at least 1–2/per year in lower-risk patients (no renal or myocardial dysfunction) to every 4–8 weeks in higher-risk patients, in keeping with guidelines on heart failure.

What level of rise in creatinine/electrolytes is acceptable when a patient starts receiving a diuretic or ACEI/ARB in heart failure or hypertension?

Creatinine

We recommend that:

- up to a 50% rise in serum creatinine from baseline may represent a physiological response
- a creatinine rise of <30% would not normally require action
- a creatinine rise of 30–50% (or to >200 μmol/l/eGFR <30 ml/min) should prompt clinical review of volume status, and temporary dose reduction or withdrawal of diuretics (if hypovolaemic) or of the ACEI/ARB[18]
- a rise of >50% or to >256 μmol/l (eGFR approxinmately 20–25 ml/min) should normally prompt dose reduction or withdrawal of diuretic (if hypokalaemic) and/or stopping ACEI/ARB pending further investigation or referral for concurrent treatment with diuretic and ACEI/ARB; the ACEI/ARB can be restarted if renal insufficiency improves after reduction or withdrawal of diuretic.[19]

We recommend the same retesting intervals (ie, 5–7 days until stable) as when initiating treatment and the same threshold (<30% rise) for considering reintroduction.

If the potassium (K^+) concentration is >5 mmol/l before treatment, treatment with any drug that may increase the serum potassium should normally only be initiated with specialist advice.

Stable K^+ increases to ⩽6 mmol/l do not usually require change in treatment, although:

- rises to 5.5–5.9 mmol/l should prompt more frequent monitoring
- if it rises >6 mmol/l, all drugs that may increase potassium and concomitant nephrotoxic drugs should be stopped and specialist advice sought.[1 20]

Nephrology advice is recommended when:

- there is uncertainty about impaired or deteriorating renal function[6] especially if creatinine increases 50% above baseline[14]

- the eGFR is <30 ml/min
- the serum sodium falls to <132 mmol/l (persistent after water restriction if clinically applicable)[6]
- any serious hyperkalaemia (K^+>6 mmol/l) develops on treatment
- strong clinical grounds exist for continued drug use in the presence of rising potassium to levels requiring dose reduction.

BACKGROUND

A rise in urea and creatinine is expected when a patient starts receiving ACEI because of a complex interaction of the renin–angiotensin–aldosterone system and renal vasculature. This interaction can lead to a decrease in the GFR and an impaired potassium excretion in some patients. Diuretics likewise affect kidney function via an intrinsic renal feedback mechanism and can lead to renal impairment in some individuals. Diuretics are best used flexibly and in the minimum dose to reduce symptoms and maintain ''dry weight'' to avoid electrolyte disturbances.[6] In addition, it is advised that, to avoid renal insufficiency when the degree of diuresis exceeds the mobilisation of fluid in patients with oedema with heart failure or hypertension, the dose of diuretic is adjusted so that the patient's weight reduction does not exceed 1 kg/day.[21]

Deterioration in renal function in patients with hypertension or heart failure is often seen when either ACEI or ARB are used. In both cases, this represents a change in the effective arterial volume when the drugs are started. In most cases, a mild rise (up to 30% above baseline) will not require action. Any increases beyond this level may represent volume depletion either from overaggressive diuresis, low cardiac output—more common in patients with heart failure or bilateral renal artery stenosis—seen potentially in both hypertension and heart failure, when large falls in GFR may occur in the presence of maintained blood pressure. It is therefore advisable in these instances to review volume status. If the patient is found to be volume depleted and the patient is treated with diuretic and ACE I/ARB combination, the diuretic should be withheld before reducing or withholding the ACEI/ARB.[6 22]

If the patient is not hypovolaemic and both diuretic and ACEI/ARB are stopped or reduced, we recommend the same retesting intervals (ie, 5–7 days until stable) as when initiating treatment and the same threshold (<30% rise) for considering reintroduction, although we found no specific guidance on this topic.

In all cases of long-term deterioration in renal function, other causes of renal deterioration such as diuretic-related volume depletion, other drug effects, notably non-steroidal anti-inflammatory drugs, or other renal disease should be considered.[23]

Other guidelines relating to treatment for hypertension state that ''A limited increase in serum creatinine of as much as 35% above baseline with ACEI/ARB is acceptable and not a reason to withhold treatment unless hyperkalaemia develops''.[24] If patients are receiving a high dose of an ACEI and not volume depleted, many clinicians will reduce the dose of the ACEI if the creatinine rises 30–50% above baseline rather than stop it altogether. The European Society for Cardiology[25] consensus document recommends stopping ACEI (and by extrapolation ARB) if the serum creatinine rises to >50% or to >256 μmol/l.

Patients with hypertension with coexistent peripheral vascular disease, suspicion of renal artery atherosclerosis or clinical evidence of vascular/renal bruits should be referred for specialist evaluation before starting ACEI or ARB in view of the risk of renal artery stenosis and its related deterioration in renal perfusion after initiating treatment.[13]

Referral is recommended if there is existing renal impairment, especially if there is uncertainty about the diagnosis or the cause of deterioration in renal function.[6] As management discussion with a nephrologist is recommended for patients with stage 4 chronic kidney disease (GFR <30 ml/min),[1] decisions on ACEI/ARB treatment should flow from this discussion.

The use of an ARB in patients previously intolerant of an ACEI (because of hypotension, hyperkalaemia or renal dysfunction) need to be more carefully monitored during treatment and any subsequent dose titration. Recently, the use of a combination of ACEI and ARB has been trialled more so in heart failure[26]; this approach will usually be under specialist care and again will require more careful monitoring of blood chemistry than the recommendations given.

Hyperkalaemia is asymptomatic and potentially dangerous. Patients will often become hyperkalaemic while on treatment with ACI inhibitors/ARB or with diuretics that ''spare'' potassium (eg, amiloride, spironolactone); this adverse effect is potentiated by any degree of renal impairment. Many other factors may increase the risk of hyperkalaemia, including the use of non-steroidal anti-inflammatory drugs, heparin or β-blockers; the presence of diabetes mellitus; advancing age; concurrent illnesses especially with dehydration; and the use of ''low-salt'' substitutes. The potassium level is usually measured before any drugs are given that could potentially increase the level. Caution is recommended when prescribing these drugs if the serum potassium is >5 mmol/l, and we suggest that specialist advice be sought in these cases to reduce risk to patients. A subsequent rise in the potassium level is likely, and monitoring is important until the level has reached a plateau. A rise to >6 mmol/l necessitates stopping all drugs that that may increase potassium[1] and concomitant nephrotoxic drugs; specialist advice should be sought.[19]

GMS contract indicator: none specific to these situations, although indicators have been introduced for chronic kidney disease.

RHEUMATOID FACTOR AND HUMAN LEUCOCYTE ANTIGEN B27 IN THE INVESTIGATION OF INFLAMMATORY JOINT PAIN (PCD, RH, WSAS, GPS)

These questions consider two common clinical scenarios in primary care: diagnosis and monitoring of rheumatoid disease in small joint pain (PCD and RH), and the utility of the human leucocyte antigen (HLA) B27 in the investigation of low back pain (WSAS and GPS). They highlight the limitations of both these tests as diagnostic markers, and the need for a clinical filter designed to distinguish inflammatory from other mechanical joint pain before further investigation. In particular, they also show that repeat measurement of RhF seems to have no role in patients with rheumatoid arthritis.

What information does rheumatoid factor (RhF) measurement provide in the investigation of multiple small joint diseases and in whom should I measure it? We recommend measurement of RhF:

- only in patients with evidence of inflammatory arthropathy (raised erythrocyte sedimentation rate (ESR) or C reactive protein (CRP), joint swelling or damage)
- as part of the diagnosis of rheumatoid disease, for diagnostic and prognostic purposes.

Rheumatoid factor (RhF) can be measured by a number of differing assays, with variation in quantitation, sensitivity and specificity.

The type of assay used will determine its usefulness. Agglutination assays are less sensitive and are mainly used

for screening purposes. Nephelometric assays and ELISA are more sensitive and provide a quantitative measure of RhF. Your local laboratory will be able to provide further information on the assay used.

There is agreement that although RhF is present in 70–90% of patients with rheumatoid arthritis, its absence does not exclude rheumatoid arthritis although these patients have a milder disease.[27–29]

A positive RhF at low titre is found in a variety of diseases, particularly immunological disorders, infectious diseases and haematological malignancies.[27–29]

RhF is used as a criterion in the American Rheumatism Association guidelines for the diagnosis of rheumatoid arthritis, but the assay variability means that there is a requirement for any assay to be positive in <5% of a control population.[28 30]

When the assay is performed at its optimum, it achieves a sensitivity of 80% and a specificity of 95%. It is considerably affected by the pretest probability. The overall prevalence of rheumatoid arthritis in the population is 0.8%. Using an assay that complies with the American Rheumatism Association guidelines, this gives a positive predictive value of RhF of 10%; it is therefore unsuitable for population screening.[27 28]

In instances where an inflammatory arthopathy is present (raised ESR or CRP, joint swelling or damage), the positive predictive value rises to >75% and the negative predictive value is around 90%, making the test a useful diagnostic aid, providing an appropriate assay method is used.[27 28]

The prevalence of RhF increases with age, and 10–20% of people >65 years will be seropositive.[27 28]

The titre of the RhF is, in addition, an important predictor of severity of rheumatoid arthritis, and high titres (>100 IU) are associated with the development of radiographic erosions and extra-articular manifestations.[29 31–33]

Other antibody subtypes (IgG and IgA) have not found a place in the routine investigation of rheumatoid arthritis. There are reports of more severe disease associated with the presence of IgA RhF.[27 34]

RhF is useful in the diagnosis of rheumatoid arthritis when inflammatory arthropathy is present but cannot be used as a screening test. It provides prognostic information on the severity of the disease and the likelihood of erosions and extra-articular manifestations. Other subtypes have not proved useful in managing the disease, but further studies are required.

Should I repeat RhF measurement to obtain information in the monitoring of rheumatoid disease?

We do not recommend use of RhF in monitoring rheumatoid disease.

The measurement of RhF varies depending on the assay used. The only quantitative assays statistically consistent enough for monitoring purposes would be nephelometry and ELISA methods.

However, no studies are convincing enough to show that even using a precise assay the level of the RhF has more than a weak association with the disease process.[35–37]

There is a slow change in RhF in association with disease-modifying drugs such as penicillamine. This drop, although important, does not correlate with changes in ESR or joint score.[35–37]

Possible reasons for this poor correlation are:

- the circulating level of RhF does not reflect the tissue or joint level
- the RhF is a byproduct of a disease process rather than a causative agent. Newer assays including cyclic citrinullated peptide[37] suggest this may be the case
- measurement of IgM RhF does not adequately reflect the total mass of complexes as it does not include contributions from IgG and IgA.

There has been a report of the loss of RhF before the development of lymphoma in patients with Sjogren's syndrome, but further studies are required before its use can be recommended.[38]

RhF therefore adds no information in the monitoring of rheumatoid arthritis, and alternative assays such CRP as a marker of inflammation should be used if a marker of disease activity is needed.

When should I test for HLA B27 in a patient with back pain?

We recommend that:

- B27 testing not be requested in primary care
- criteria for specialist advice/referral should rather be based on the presence of inflammatory back pain defined as ⩾3 of the following features:
  - back pain persisting for ⩾3 months
  - back stiffness, especially in the morning, lasting for at least 30 min
  - age of onset <40 years
  - insidious onset of back pain
  - back pain improved by exercise.

The human leucocyte transplantation antigen B27 is associated with ankylosing spondylosis and is present in about 90% of white and 50% of black patients with ankylosing spondylosis and other spondyloarthritides (SpA), many of which may represent early forms of ankylosing spondylosis.[39 40] However, it is insensitive as a test alone (20% sensitivity), as many people with the B27 antigen do not develop ankylosing spondylosis and B27 has a high prevalence in many populations.

Although radiological evidence of sacroileitis is reported to be the most specific and consistent finding in ankylosing spondylosis, it may be absent in early disease and in SpA.[41]

Several recommendations for B27 testing suggest restricting its use to atypical patients with symptoms of inflammatory back pain associated with radiological sacroileitis, or in patients without radiological sacroileitis otherwise likely to have ankylosing spondylosis (eg, uveitis and back pain).[42–45]

The presence of inflammatory back pain used by the European Spondyloarthropathy Study Group[46] and based on Clin's questionnaire[47] can be defined by ⩾3 of the following features:

- back pain persisting for ⩾3 months
- back stiffness, especially in the morning, lasting for at least 30 min[48]
- age of onset <40 years
- insidious onset of back pain
- back pain improved by exercise.

A recent review of published findings for ankylosing spondylosis and SpA found that presence of inflammatory back pain seems to raise the average background probability of SpA from 5% to 14% in patients with chronic back pain.[49] When combined with positive B27 measurement, the positive predictive value for SpA was found in this review to be to 54%, rising to 90% and more if other clinical features (anterior uveitis, enthesitis) are present. This seems to have reopened the debate about the targeted use of B27 in clinically equivocal situations in suitable populations.[50–52]

However, the permutations of clinical scenarios and population differences render this test of limited use in a primary care context, particularly as the principal discriminator for SpA is inflammatory back pain.

Patients with SpA respond to the same appropriate anti-inflammatory and other newer specific treatments as those with ankylosing spondylosis. There is still, however, no clear evidence that early identification of patients with SpA, estimated to represent potentially 5% of patients with primary care chronic back pain,[53] will lead to improved long-term outcome, although accurate identification will help to focus treatment.

Use of the test is further limited by the fact that pretest and post-test probabilities also vary greatly between populations, however, because of large differences in both the prevalence of B27 in populations and the prevalence of B27 among patients with spondylarthropathy.[45]

The test is comparatively expensive and is not suitable for use as a screening or diagnostic test.

Testing is for HLA B27 in primary care is not currently appropriate, and discussion with a specialist rheumatologist is advisable if a spondyloarthropathy is suspected. B27 testing if performed would normally form part of secondary care assessment.[54]

GMS contract indicator: none.

LABORATORY INVESTIGATION OF CHRONIC DIARRHOEA (GH, DGW, PJG)

These questions divide the investigation of chronic diarrhoea simplistically between causes in adults and those in children. Although a clear overlap exists, the prevalence of causes varies both between the age groups and within individual groups. There are so many possible causes of diarrhoea and presenting clinical situations that it is not possible to establish a single set of recommendations, and what emerges from the reviews identified is the need for a detailed clinical filter to guide further investigations. There is also no absolute boundary between investigations that would normally be requested in a primary and secondary care setting, and a division is offered based on author opinion. This answer considers diarrhoea in the context of chronic bowel disease, excluding colorectal carcinoma, which if suspected clinically would be referred for urgent secondary care assessment. A separate question will examine the utility of faecal occult blood testing.

What initial screening investigations are used to investigate chronic adult diarrhoea in primary care in the UK?

We recommend, once chronic diarrhoea has been confirmed, if the cause is not clinically apparent from a clinical filter:

- full blood count (FBC), vitamin B_{12}, folate, urea and electrolytes, liver function tests calcium, ferritin, ESR or CRP and IgA endomysial antibodies, glucose (fasting) and thyroid function
- a stool sample for microbiology investigations if recent foreign travel was undertaken
- subsequent endoscopic investigations depending on clinical presentation.

Chronic diarrhoea is common, affecting between 4% and 14% of adults.[55 56]

The first step in investigation is to confirm that the presentation is chronic not acute. This may be defined as the abnormal passage of $\geqslant$3 loose or liquid stools/day for $>$4 weeks and/or a daily stool weight of $>$200 g/day.[57] As stool weight is currently rarely performed and symptom reporting may vary, considerable potential exists for overlap between functional and organic bowel disease.

Once confirmed, a detailed history for risk factors for organic disease and/or reported symptoms (blood or mucus in stool, abdominal pain) will guide further investigations (organic as opposed to functional disease, family history, previous surgery, use of ethanol or drugs, antibiotic treatment and recent overseas travel).

The screening tests recommended have high specificity for organic disease in a small cohort of patients with normal stool and colonic investigations,[58] but was only 62% sensitive for detecting disease. Normal screening tests do not therefore exclude organic disease, nor do the existing positive and negative symptom criteria.[59–61]

ESR or CRP are specific but insensitive indicators of chronic inflammatory disease.[62]

FBC, urea and electrolytes, liver function, vitamin B_{12} and folate, calcium and iron studies will provide evidence of possible malabsorption.[57] The presence of iron deficiency is also a non-specific indicator of small-bowel enteropathy, particularly celiac disease.[63]

The British guidelines[57] recommend that routine screening for coeliac disease (currently with IgA endomysial antibodies) be performed in view of the high prevalence of the disease in Western countries.

If evidence of malabsorption is found, the British guidelines also recommend specific testing (eg, faecal elastase as a test for pancreatic insufficiency) in view of the difficulties and decreasing availability of 3-day faecal fat measurement, and uncertainty as to the diagnostic utility of other primary faecal investigations.

Systemic diseases such as thyrotoxicosis, parathyroid disease, diabetes mellitus and adrenal disease may also be a cause of chronic diarrhoea via a variety of mechanisms including endocrine effects, autonomic dysfunction, bacterial overgrowth or the use of concomitant drug treatment.[64]

Chronic diarrhoea due to infectious agents is rare in the developed world, but may be considered where there has been a history of travel to high-risk areas. Protazoan infections such as giardiasis and amoebiasis are the most common parasitic causes of chronic diarrhoea in travellers.

What initial screening investigations are used to investigate chronic childhood diarrhoea in primary care in the UK?

We recommend:

- detailed history and careful anthropometric assessment from historical records
- careful dietary history dealing with any anomalies
- further investigations in children not growing or acutely unwell are usually undertaken in secondary care.

Simple investigations that might be considered if samples can be collected and the stool samples delivered to the laboratory within 3 h are:

- stool sample for parasites
- faecal-reducing substances
- faecal elastase (or chymotrypsin)
- blood sample (if considered appropriate) for
  - FBC
  - endomysial antibodies
  - ferritin
  - alkaline phosphatase.

Chronic childhood diarrhoea can be defined as the passage of ⩾4 watery stools per day persisting for at least 2 weeks.[65 66] In most instances, the protracted diarrhoea seems to follow an episode of acute gastroenteritis in early infancy, which has sensitised the intestine to foreign proteins, especially milk (secondary lactose intolerance).

A detailed clinical history and anthropometric assessment is essential. Blood in the stool should lead to prompt referral to secondary care to exclude chronic infections (eg, giardiasis or underlying immunocompromise), intestinal polyps or inflammatory bowel disease.

Toddler diarrhoea, commonly referred to as ''peas and carrot diarrhoea'' is the most common form after gastroenteritis in infants. It probably extends on to childhood and is associated with some discomfort—a variety of treatment approaches including stress reduction showing effect. The primary feature is that the child appears healthy and is growing normally. In some children, a family history of irritable bowel syndrome may be found.

A dietary history should check for excess intake of fruit juices, squash, fizzy drinks, sugar-free gum or boiled sweets. Concomitant respiratory disease or recurrent infections should prompt consideration of cystic fibrosis or immunocompromise. A history of foreign travel outside western Europe would widen possible aetiologies.

Further investigations are normally not considered necessary for ''routine'' acute non-severe diarrhoea, although they are recommended in complicated cases: bloody diarrhoea, suspected food poisoning, systemically ill children or recent foreign travel.[67–69] The effect of testing on outcome does not seem to have been subjected to randomised clinical trials.

The decision to refer to secondary care will be governed by the child's age, growth records and severity of symptoms.[65] This guidance, therefore, is restricted to laboratory tests to identify the most common classes of aetiology in primary care and to assist in the referral decision. In practice, this can be summarised by initial investigations designed to discriminate functional diarrhoeas from food intolerances, infectious and post-infectious diarrhoea, inflammatory colitis and malabsorption (fig 1).

Further investigation of malabsorption and the diagnosis of enteropathies relies greatly on endoscopy and/or biopsy,[65 70 71] and would therefore be expected to take place in a secondary care setting.

Infectious or parasitic diarrhoea may be suspected from a clinical history of foreign travel, contact with animals or contact with infected children. Examination of fresh stool or parasites (three consecutive days, submitted to the laboratory within 3 h) will identify three quarters of cases of giardia infestation.[72] Diarrhoea is unlikely to become persistent after bacterial or viral infection except in the situation of post-infectious enteritis, which although less uncommon in Western populations[67] makes up a large proportion of cases of infantile enteritis.[71]

Children with post-infectious disaccharide intolerance usually respond to an exclusion diet of milk and egg. The success often involves good paediatric dietetic input and hence referral.

Further investigation might be considered, but can equally be performed in secondary care. Malabsorption, particularly due to cystic fibrosis, may be screened for by measurement of faecal elastase (or chymoptrypsin) or faecal microscopy for fat globules on three samples, either sent freshly or frozen till dispatch. Carbohydrate intolerance including inherited defects in the gut endothelium, such as sucrose-isomaltase deficiency, manifest with faecal-reducing substances, again in a fresh (or promptly frozen) sample.

If the child is old enough and venepuncture is considered reasonable in primary care, a sample for either anti-endomysial antibodies (with IgA to exclude concomitant IgA deficiency) or anti-tissue transglutamase antibodies offer a high sensitivity and specificity for coeliac disease. Measurement of FBC, ferritin and alkaline phosphatase offers a simple screen for evidence of malabsorption of iron and vitamin D (although alkaline phosphatase may require laboratory advice for interpretation in children in the context of age and maturity status before considering vitamin D measurement).

GMS contract indicator: none.

MUMPS AND CHICKENPOX (WI, KK)

These two questions are the first of a set of four examining common situations of potential viral infection in primary care, and the need or otherwise to use diagnostic laboratory testing. In some instances, several different methods are available to diagnose the infection. Where possible, guidance is reported on which method is considered preferable, although diagnostic approaches may at present vary between laboratories.

What tests should I carry out if a pregnant woman has been in contact with chickenpox or shingles?

We recommend:

- asking for a personal history of chickenpox
- if no history is forthcoming, then send clotted blood for varicella-zoster virus (VZV) immunity testing
- if significant contact and VZV immunoglobulin negative, passive immunisation should be offered

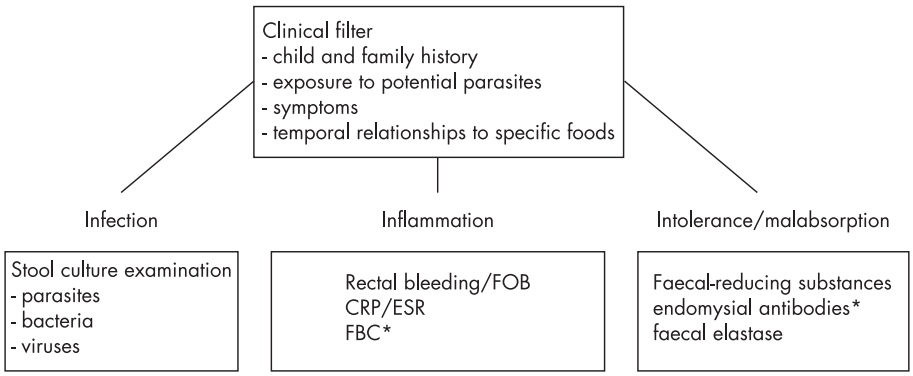

Figure 1 Suggested algorithm for primary care investigation of persistent diarrhoea (adapted from Knight and Sandhu[69]). *, If clinically indicated; CRP, C reactive protein; ESR, erythrocyte sedimentation rate; FBC, full blood count; FOB, faecal occult blood.

- if a rash has already developed (specific cases are discussed in the text).

The clinical problem is that a susceptible woman who is in contact with chickenpox or shingles may acquire infection. Primary VZV infection in pregnancy carries a risk of life-threatening varicella pneumonia to the mother. This is more common in a pregnant than in a non-pregnant woman. Risk factors for severe lung involvement include smoking and a more extensive rash (defined as >100 skin lesions).[73 74] The virus may also cross the placenta and infect the fetus, which may give rise to the fetal varicella syndrome, also known as varicella embryopathy.[75] There are protean manifestations of this, the most distinctive of which are extensive areas of skin scarring and failure of limb bud development. The risk is of the order of 1–2% in women with chickenpox in the first half of pregnancy.[75] Fetal damage arising through maternal varicella at 20–28 weeks gestation has been described in isolated case reports, but is rare.[76] Finally, maternal varicella occurring at the end of pregnancy (ie, within 7 days before and after delivery) may result in the baby acquiring neonatal varicella, which has a considerable mortality.

Management of a pregnant woman in contact with chickenpox or shingles hinges on whether she has already been infected with VZV. The simplest way to elicit this is to ask about a history of chickenpox; if this is clearly established, she can be reassured that there is no risk arising from her recent contact, as second epsiodes of chickenpox are extremely unusual, and no adverse events from them in pregnancy have yet been described.[73] If the history is unclear, the next step is to test a serum sample for the presence of IgG to VZV. Laboratories should be able to generate a result within 24–48 h of receiving the sample. Most women (well over 80%) of child-bearing age in the UK have such antibodies even if they do not recall the episode of chickenpox,[77] although this figure is lower for women born and raised in tropical or subtropical areas.[78] Antibodies detected within 10 days of contact indicate past infection (or immunisation) and can used to provide reassurance of no risk.

If the patient has no history of chickenpox, and a serum sample is shown to be negative for VZV antibodies, then recommended management is to offer passive immunisation with varicella-zoster immunoglobulin (VZIG), prepared from pooled plasma from donors with high titres of varicella antibodies), provided the contact is significant, and within 10 days.[79] Significant contact is defined as being in the same room as someone with chickenpox for 15 min, having face-to-face contact with someone with chickenpox (eg, a conversation) or living in the same household.[79] An individual with chickenpox or disseminated zoster is infectious for 48 h before the onset of the rash until the lesions have crusted over. An individual with exposed zoster (eg, ophthalmic zoster) should be regarded as infectious from the day of onset of the rash until crusting has occurred.[79]

About 50% of susceptible women given VZIG will develop clinical varicella, although the disease may be attenuated and a further 25% will develop subclinical infection.[79] Patients who have received VZIG on a previous occasion should be retested for VZV antibodies in the event of another relevant exposure to chickenpox or shingles. There is also evidence that VZIG reduces the risk of transplacental transmission of VZV, which will thereby reduce the risk of embryopathy.[74] These women should be advised of the potential risks of fetal varicella arising from their infection. Serial ultrasound monitoring of the fetus may allow identification of the abnormalities associated with varicella embryopathy at a time when it is possible to offer termination.

VZIG is of no benefit if a pregnant woman presents with chickenpox. The Royal College of Obstetricians and Gynaecologists guidelines state that in this setting, oral aciclovir should be recommended to women >20 weeks of gestation on the first day of the rash, with informed consent, whereas for women <20 weeks gestation, aciclovir should be offered.[73] If maternal chickenpox develops within 7 days of delivery, the neonate should be given VZIG and the use of prophylactic aciclovir considered, to reduce the risk of life-threatening neonatal varicella.[79]

GMS contract indicator: none.

When should I test for mumps, and should I notify mumps infection?

We recommend:

- testing for mumps virus infection in cases clinically compatible with the disease
- mumps virus infection is a notifiable disease in the UK.

Mumps virus infection may present as asymptomatic seroconversion (ie, subclinical infection) in about 30% of infections.[80]

After an incubation period of 14–21 days, a prodromal illness may occur with malaise, myalgia, low-grade fever, headache and lasting for 1–2 days before the onset of parotitis, which occurs in 95% of symptomatic disease, and is bilateral in 75% of cases. Glands are swollen and tender, duct orifices red and oedematous. Swelling lasts for 4–7 days. Submandibular and sublingual glands are occasionally involved. Patients are infectious from 7 days before to 9 days after the onset of parotitis.

Complications include central nervous system involvement: aseptic meningitis (5–10% cases, men more often than women), meningoencephalitis (about 1 in 6000 cases), which may cause convulsions, focal neurological signs, motor or sensory disorders, and hearing loss, which may occur in the absence of meningitis or encephalitis; orchitis, epididymitis, oophoritis (said to occur in up to 40% and 5% of post-pubertal men and women, respectively); pancreatitis (usually not severe); and rarely, arthritis and myopericarditis.

Central nervous system manifestations may occur in the absence of clinically evident salivary gland disease.

Infection during pregnancy may increase the risk of spontaneous miscarriage, but a congenital mumps syndrome has not been described.

The clinical diagnosis of mumps may be unreliable, and cases are rare especially in populations with a low incidence. One study in Australia reported laboratory confirmation of only 9% of all notified mumps cases.[81] The positive predictive value of the clinical case definition was only 10%.

Mumps is a notifiable disease in the UK, and therefore all clinically suspected cases should be reported to the local Consultant for Communicable Disease Control. Monitoring of infection is important in determining appropriate immunisation policies; there have been a number of outbreaks of mumps among young adults in the UK over the past 5 years and a large increase in notified cases.[82]

For reasons outlined earlier, it is therefore important to confirm a clinical diagnosis of mumps virus infection by sending appropriate specimens for laboratory confirmation. Several laboratory methods exist to diagnose mumps infection. It is possible to detect mumps IgM in saliva samples for up to 5 weeks after acute infection.[83] Detection of mumps-specific IgM in an acute serum sample, or a rising titre of mumps IgG in paired acute or convalescent sera, can also be used to confirm the diagnosis. Finally, a buccal or throat swab, broken off into viral transport medium, can be used to isolate the virus or

detect viral RNA. The virus is excreted in saliva for up to 2 weeks, and in urine for up to 3 weeks after acute infection.

In the UK, the Health Protection Agency offers oral fluid testing for mumps IgM, which can be performed via a salivary kit obtained from laboratories. Local practices may however vary, and practitioners should establish the local methods in use from their microbiology/virology services.

GMS contract indicator: none.

CONCLUSION

This review brings to a running total of 77 question and answer sets written to provide an overview of current advice in the use of laboratory tests in primary care. Answers to the first four question answer sets can be found in Smellie *et al*.[84–88] They have all used a common search method,[89] although in instances where recent systematic reviews have been performed, the guidance also relies heavily on the findings of these reviews. Authors wishing to consult the UK General Medical Services Contract and the current Quality and Outcomes Framework guidance can find these on their respective websites.[90 91]

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