REVIEW

Best practice in primary care pathology: review 5

W S A Smellie, J Forth, S Ryder, M J Galloway, A C Wood, I D Watson

J Clin Pathol 2006;59:1229–1237. doi: 10.1136/jcp.2006.037754

This fifth best practice review examines three series of common primary care questions in laboratory medicine: (1) minor liver function test abnormalities; (2) laboratory monitoring of patients receiving lithium; and (3) investigation of possible venous thromboembolism. 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 fifth in a series of reviews which answers several questions that arise during the use of pathology in primary care.

Each topic is introduced with a brief summary of the type of information found and is handled separately.

Although the individual topics are not related because 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 issues in the primary care laboratory, 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.

MINOR LIVER FUNCTION TEST ABNORMALITIES (WSAS, SR)

Biochemical tests of liver function are used to investigate a wide range of symptoms and for various purposes in asymptomatic people. This raises the potential to discover significant disease at an early stage in its natural history, but also produces abnormal results in apparently healthy people. This is particularly so in the “statin prescribing” era.

The usual liver function tests include two separate types of tests. Serum albumin and bilirubin provide a true measure of hepatic function, although both can be abnormal for several non-hepatic causes. The remaining tests are of liver enzyme levels, usually alanine

aminotransferase (ALT) or aspartate transaminase (AST) in combination with alkaline phosphatase (ALP) +/- γ -glutamyl transpeptidase (GGT).

These answers attempt to allow the user to identify situations in which values of one or more of these tests outside the 95% population reference range (mean (2 standard deviations (SDs)) for the population) may indicate the presence of clinically significant disease.

In view of the statistical phenomenon of regression to mean,¹ the principle of interval retesting to establish one-off from stable and progressive increases seems sound. There is guidance, but limited evidence, on retesting intervals, although in the asymptomatic context and in view of the slow time course of the potential underlying diseases, the retesting interval of months rather than weeks seems reasonable for minor increases, commonly described as up to 3–5 times the upper limit of normal (ULN). Indications for further investigation of persistent rises commonly refer to 1.5 ULN. The limitations of reference ranges are further compounded for liver tests by the fact that population results are not normally distributed and exhibit a right skew effect.

How should I investigate an isolated slightly raised alkaline phosphatase in an asymptomatic adult?

We recommend:

- Checking of liver and bone profiles if not already carried out, to exclude other raised indices.
- Isolated raised values up to approximately 20% above the ULN (typically 120 IU/l) are more likely to reflect a statistical rather than clinical finding.
- If <1.5 ULN: recheck in 1–3 months.
- If >1.5 ULN (2 measurements, 6 months apart): further investigation indicated.
- If >3 ULN (single measurement): further investigation indicated.

Reference ranges of ALP are age and sex-related, being lower in women than men, but rising in women beyond middle age. In addition, bone-specific ALP is higher in black women than in white.² Laboratory methods and reference ranges unfortunately vary by method, and users should acquaint themselves with local ranges.

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate transaminase; BNF, British National Formulary; DVT, deep venous thrombosis; GGT, γ -glutamyl transpeptidase; GMS, General Medical Services; NAFLD, non-alcoholic fatty liver disease; ULN, upper limit of normal

See end of article for authors' affiliations

Correspondence to:
W S A Smellie,
Department of Chemical
Pathology, Bishop
Auckland General
Hospital, Cockton Hill
Road, Bishop Auckland,
County Durham DL14
6AD, UK;
info@smellie.com

Accepted 20 February
2006
Published Online First
19 May 2006

The laboratory reference range contains 95% of the population values. Notwithstanding exceptions described earlier, 2.5% of people would therefore be expected to have activities above the ULN, and, in view of the low prevalence of disease in patients with minor rises just over the mean (up to approximately 20%), this is more likely to represent a statistical rather than a clinically relevant finding. Using a typical local reference range of 35–104 IU/l, approximately 2.5% of a normal population will be expected to have values >104 IU/l (mean (2 SDs)), compared with approximately 0.1% >121 IU/l (mean (3 SDs)).

ALP has two main sources in the non-pregnant adult: liver and bone.

Higher ALP activities are also seen as a normal variant³ and are associated with a range of medical conditions (congestive heart failure, hyperthyroidism, pregnancy) and certain drugs (ibuprofen, acetaminophen, cefotaxime) (reviewed in Aranda-Michel and Sherman²).

Liver

ALP is an intrahepatic cannalicular enzyme, which when raised because of liver disease reflects intrahepatic or extrahepatic obstruction rather than hepatocellular damage, although both may coexist.

In addition to clinical assessment of possible risk factors for, or indicators of, liver disease to distinguish potential hepatic risk factors from bone disease, GGT^{4–8} (or 5' nucleotidase when used as an alternative⁹) offers the best means of identifying a hepatic origin.

Recommendations distinguish isolated from paired or multiple-enzyme abnormalities as an initial indicator of potentially significant disease. Although not evidence-based, a threshold of 1.5 times ULN is cited by several authors as an indication for further investigation at 1–3 months if raised <1.5 ULN⁴ with further investigation if >1.5 ULN on two occasions at least 6 months apart.⁵ This is consistent with a review in the *Journal of Insurance Medicine*⁶ describing the threshold as a means of distinguishing potentially significant disease, although the same review highlights the paucity of direct clinical data relating liver enzyme abnormalities to mortality. On the basis of mathematical calculation of mortality associated with biopsy diagnoses, this review concluded that, if alcohol and hepatitis were excluded, background mortality was “fairly low” for patients with mild to moderate liver profile abnormalities.

Although the reference range for women rises with age, the prevalence of primary biliary cirrhosis also rises. Measurement of antimitochondrial antibodies in cases of persistently increased ALP >1.5 times ULN of liver origin would therefore seem appropriate.

Bone

Raised ALP without a concomitant rise in GGT in a non-pregnant adult is likely to be of bone origin.^{4–8} Formal distinction can often, but not always, be achieved by isoenzyme analysis if uncertainty remains in the presence of marked abnormalities.

Calcium studies combined with the clinical filter will help in the diagnosis of treatable bone disease due to osteomalacia and parathyroid disease, and therefore seem clinically justified. However, the most common reason for raised bone ALP in older people is (often subclinical) Paget's disease.

Paget's disease is estimated to have a prevalence of 2–6% in the UK,¹⁰ and to have autosomal dominant inheritance with variable penetrance in some families.¹¹ ALP activity is reported to correlate with disease activity, and the relative risk of Paget's disease in patients with raised ALP is 10.9, although Paget's disease was also found in 2.3% of people with normal ALP.¹²

The currently established indications for treatment of Paget's disease are based on symptoms and preparation for orthopaedic surgery.¹³ Presently, in the absence of these situations, a further investigation on minor bone-related ALP would seem unwarranted in an asymptomatic patient with normal calcium studies.

How should I investigate an isolated case of slightly raised bilirubin in an asymptomatic adult? We recommend:

- Values up to 20% above ULN are likely to be statistical rather than clinical abnormalities.
- Values <1.5 times ULN: interval retest in 1–3 months unless clinical suspicion of disease.
- Values >1.5 ULN: confirm proportion of indirect (unconjugated) bilirubin.
- If >70%, unconjugated, probable Gilbert syndrome: no further testing needed if non-progressive on interval retesting, unless haemolysis is clinically suspected. If rising on retesting, consider haemolysis and test haptoglobin, lactate dehydrogenase and blood count with reticulocyte count.
- Values >3 times ULN: clinical disease probable, further investigation required. Consider ultrasound (conjugated >50%) or haemolysis (unconjugated >70%).

As a product of the degradation primarily of haem, and excreted in bile, circulating bilirubin concentrations are determined by the balance of production and excretion.

Production is increased principally in disorders of red blood cell metabolism and excretion in disorders of hepatic conjugation (producing unconjugated or indirect bilirubin) or removal (producing conjugated or direct bilirubin). Laboratory discrimination of direct from indirect bilirubin becomes less reliable at lower total bilirubin concentrations (typically < approximately 40–50 mmol/l).

Using the same principles as for ALP and a typical range of 5–21 mmol/l, 2.5% of a population would be expected to have a total bilirubin >21 mmol/l and 0.1% >25 mmol/l. Users should again check their local ranges.

The clinical assessment should logically seek to exclude drugs that interfere in the bilirubin reaction (propranolol, oxytetracycline, methotrexate and levodopa)² and take this into account in the decision to investigate further for stable raised bilirubin.

As described earlier, a raised bilirubin in conjunction with other liver function test abnormalities will prompt further investigation directed by predominant pattern of hepatocellular (transaminases) or cannalicular (GGT and ALP) changes.

The most common cause of “slight” isolated rises in bilirubin is Gilbert syndrome, a benign untreated congenital defect of glucuronide conjugation, present in up to 5% of the population.¹⁴ This produces unconjugated raised bilirubin (particularly during intercurrent illness or fasting) usually not exceeding 68 mmol/l^{9 15} (or up to 85 mg/dl¹⁶). Although diagnostic investigations may be used to diagnose this, reassurance will in most cases be sufficient.^{9 15}

Identification of raised bilirubin in conjunction with raised cannalicular enzyme (ALP or GGT) should prompt consideration of potential intrahepatic or extrahepatic cholestasis and is not described further in this answer.

Saturation of the conjugation process by excess production of bilirubin will lead to a predominance of unconjugated bilirubin. One review describes raised bilirubin >50% conjugated and raised bilirubin >70% unconjugated as representing direct and indirect hyperbilirubinaemia, respectively.² If the rise is isolated, and predominantly unconjugated, exclusion of

Table 1 Investigations in asymptomatic patients with increased liver enzyme level

Test	Abnormality	Interpretation
Level 1		
Full blood count	Macrocytosis Thrombocytopenia	Suggests alcohol excess if GGT also raised Possible hypersplenism (portal hypertension)
Autoantibodies	AMA positive, IgM ASM/ANA positive, IgG	Probable primary biliary cirrhosis Strongly suggestive of autoimmune hepatitis
Ferritin	Elevated	Possible haemochromatosis, seek advice if raised
Hepatitis B surface antigen	Positive	Implies chronic infection
Hepatitis C antibody	Positive	Suggests chronic infection
Level 2		
Liver ultrasound	Mass/dilated ducts	Tumour/stones
Anti-endomysial antibodies	Positive	Suggests coeliac disease
α 1-Antitrypsin level	Low	Suggests deficiency. Phenotype required (PiZZ or PiM implicated)
Others: for example, caeruloplasmin, urine copper as dictated by clinical context	Low	Wilson's disease

Adapted from the American Gastroenterology Association.²⁴

Level 1 suggested first investigation set; Level 2, if no diagnosis obtained after Level 1.

AMA, antimitochondrial antibody; ANA, antinuclear antibody; ASM, anti-smooth muscle actin monoclonal antibody; IgM, immunoglobulin M.

increased haem turnover leaves a highly probable diagnosis of Gilbert disease. No further investigation is recommended if bilirubin concentrations fall or do not continue to rise on interval retesting. The British Columbian guideline recommended interval retesting of 1–3 months for rises in any liver test <1.5 ULN. This is consistent when there is a small bilirubin rise in an asymptomatic patient, particularly in light of the bimodal serum decrease time, which has a long terminal phase (due to δ -bilirubin formation¹⁷). Common sense would suggest that, in this period, retesting be carried out in the earlier part for larger rises and later for smaller rises. It would be unlikely to see large rises in bilirubin—for example, > 3 ULN—in the absence of other changes, and a laboratory opinion would seem reasonable in this instance (author interpretation).

Haemolysis is conventionally diagnosed by the laboratory appearances on a blood film, combined with reduced haptoglobin, reticulocytosis and raised lactate dehydrogenase. There is no clear evidence as to whether one or all of these tests are required.

If evidence of haemolysis is found, further investigation will be determined by the clinical context, usually in conjunction with secondary-care advice or referral.

Resorption of large haematomas can produce a similar pattern of hyperbilirubinaemia; this should be clinically apparent provided requesters of tests are aware of this as a possible cause.

Several recommendations for liver function testing are focused on patients with risk factors for, or clinical evidence of, suspected liver disease.^{4–8} None recommend general population screening, an approach that is also not considered to be cost effective.¹⁸

How should I investigate abnormal transaminases in asymptomatic patients without risk factors for, or clinical features of, liver disease?

- If raised <3 ULN: recheck in 1–3 months
- If still raised (two measurements, 6 months apart): further investigation indicated as shown in table 1.
- If >3 ULN (single measurement); further investigation indicated as shown in table 1.

AST and ALT are sensitive markers of hepatocyte injury but both, particularly AST, are also found in decreasing concentration in cardiac muscle, skeletal muscle, kidney, brain, pancreas, lung and blood cells. As transaminases are present

in highest concentrations in the liver, large increases are usually due to hepatocyte injury.

Serum ALT activity varies with age, sex, race, body mass index, acute illness and exercise (reviewed in Gianni *et al*¹⁸ and Giboney¹⁹), and compelling evidence from diseases such as hepatitis C, non-alcoholic fatty liver disease (NAFLD) and haemochromatosis suggest that considerable liver injury may be present with normal transaminase levels.^{20–21} Perhaps the most impressive evidence that ALT normal ranges are misleading comes from trials of treatment of hepatitis C virus infection (HCV) in patients with normal transaminase levels. These showed that if HCV was eradicated, the previously normal levels fell further.²²

The normal population reference range is therefore very approximate for clinical purposes. Certain chromogenic drugs may also interfere analytically (acetaminophen, tetracycline and aminosalicic acid), independently of liver injury.²³

The American Gastroenterology Association²⁴ defines a mild transaminase abnormality as up to 5 times ULN but does not define a lower limit for investigation. Several guidance documents refer to persistently raised transaminases of >1.5 ULN as warranting investigation. It has been suggested that increased levels of transaminases should either be investigated after 1–3 months⁴ or 3 months,²⁵ or that there should be a staged approach to investigation over 0–6 months.^{24–26} Some expert reviews suggest treating the most likely cause of the abnormal transaminases—that is, alcohol (by abstinence), hepatotoxic drugs (by drug cessation) and NAFLD (by weight reduction and diabetes or triglyceride control, where applicable) before more detailed investigation if transaminases remain abnormal after a period of observation^{24–26} with a referral (biopsy) threshold of 2.5 ULN.⁵

All the guidance found emphasised the importance of clinical history and examination to identify possible causes (particularly NAFLD, which is described in one study as prevalent in 23% of American adults²⁷) before proceeding to further investigation in these cases.

The prevalence of abnormal transaminases will therefore vary with the type of population studied, the threshold used to define “abnormal” and the time interval over which the results are studied. For example, when transaminases are measured as part of routine preoperative assessment for elective surgery, 0.1–0.3% of patients are found to have abnormalities if abnormal is defined as transaminases >2 ULN but 3.5% if any degree of transaminase elevation outside the population “reference” range is considered to be

abnormal.²⁸ Most data that are available deal with abnormal AST or ALT levels in subsections of American populations, based on single transaminase measurements.

There is evidence that increasing transaminase levels (AST and ALT) are directly associated with increased liver-related mortalities.²⁹ In the UK, there is also evidence that the causes of abnormal transaminases are often not investigated. When a thorough investigation is carried out, however, most patients are found to have significant disease warranting treatment or follow-up.³⁰

No single study has compared the clinical or histological diagnoses carried out at a certain degree of transaminase abnormality with those at a different level of abnormality. There is no great difference between the percentage of abnormal liver biopsies found when investigating patients with transaminases any degree above the normal range, above 1.5 times or above twice the ULN. Investigating patients with a greater than threefold increase in transaminases may result in fewer normal liver biopsies—that is, fewer false positives—but will clearly result in an under-diagnosis of significant liver disease (table 2).^{31–37} The only reason to set a threshold for investigating abnormal transaminases seems to be one of expedience. Sherwood *et al*³⁰ investigated patients with abnormal transaminases >2 times the reference range because lowering this threshold would have resulted in six times more patients to investigate, “well beyond our means of investigation”.

Table 1 shows an appropriate panel of initial investigations. There is no evidence to suggest that the level of enzyme abnormality in asymptomatic people has any influence on this risk of finding appreciable abnormalities on further investigation. In view of the poor correlation between the level of rise and biopsy findings, we do not recommend a lower threshold for carrying out basic investigations as shown in table 2 on persistently abnormal results.

As non-alcoholic and alcoholic fatty liver diseases are the predominant causes, these can reasonably be sought from the clinical history before proceeding to more detailed (level 2) investigations.

How should I investigate abnormal transaminases in patients with risk factors for, or clinical features of, liver disease?

- Further investigations are advised for any enzyme rise associated with risk factors for, or clinical evidence of, liver disease except where an apparent cause is found (hypertriglyceridaemia, diabetes, alcohol and overweight) for which a 6-month trial of appropriate intervention is recommended.

An asymptomatic person found to have abnormal liver enzymes should have a history taken for specific factors that may predispose to liver disease or suggest another cause. Alcohol consumption, prior medical interventions, such as surgery or transfusion, intravenous drug use or tattooing should be included, as should a detailed drug history, including non-prescribed or herbal remedies.

Physical examination aims to detect stigmata of chronic liver disease, spider naevi, clubbing, hepatomegaly or splenomegaly. If present, these suggest significant liver disease, as these signs are rarely present in the absence of hepatic cirrhosis.

The history and examination should also aim to exclude non-hepatic causes for liver enzyme increase. The most common causes that may be difficult to diagnose clinically are right-sided heart failure or constrictive pericarditis, which can cause considerable hepatomegaly and abnormal liver tests with relatively modest symptoms, and endocrine disorders, notably obesity, diabetes and thyroid dysfunction.

There is good evidence that obesity³⁸ and diabetes³⁹ cause abnormal liver enzymes via fatty liver, and the risk of death from liver disease was increased in the Verona Diabetes Study³⁹ in patients with abnormal liver function tests. The condition is benign in those with simple steatosis⁴⁰ although 10–30% of patients with considerable inflammation and particularly with fibrosis on index biopsy may progress to cirrhosis in 10 years.^{40–41} As yet, there is no specific medical treatment for NAFLD. Progressive weight loss can normalise liver enzyme levels and although there is no evidence that this improves long-term outcome, it seems logical from a general health perspective. Note, however, that starvation dieting can also cause fatty liver.⁴²

Risk factors for development of NAFLD, such as hypertriglyceridaemia and diabetes, should be dealt with, and a programme of exercise and weight reduction tried before liver biopsy is offered.

Further investigation is recommended if abnormal liver enzymes of any level are found in the presence of a major risk factor for liver disease or in particular if patients have stigmata of chronic liver disease.^{4–5 19 24}

How should I investigate abnormal GGT in asymptomatic patients without risk factors for, or clinical features of, liver disease?

- GGT has limited use as a primary liver test. Its use is recommended in particular to establish the likely origin of a raised ALP.
- No clear consensus is found on thresholds for further investigation.

In the absence of guidance we recommend that:

Table 2 Findings on liver biopsy for abnormal transaminases

Exclusions	Definition of abnormal	No	% of abnormal biopsies	% with fibrosis/cirrhosis	% with normal liver	References
None	AST and ALT >1.5× normal, >6 months	149	98.7	9/9	1.3	Minuk ⁵
None	ALT >normal, >6 months	150	96.7	58–74/4	3.3	Titcomb ⁶
None	AST and ALT >normal	83	88	14 fibrotic	12	Pratt and Kaplan ⁷
HBV, alcohol, drug induced	AST 3–8× normal, >6 months	47	100	16 fibrotic	0	Giannini <i>et al</i> ⁸
HBV, HCV, alcohol, GH, AICAH, PBC, α ₁ AT, sarcoid Wilson's	AST or ALT >1.5× normal, >6 months	81	90	4/2	10	Green and Flamm ⁹
HBV, HCV, alcohol, GH, AICAH, PBC, α ₁ AT, Wilson's	AST or ALT or ALP >1.5× normal, >6 months	36	94.4	Not stated	5.6	Cooper <i>et al</i> ¹⁰
HBV, HCV, alcohol, GH, AICAH, PBC, α ₁ AT, Wilson's	ALT, ALP or GGT >2× normal, >6 months	354	94	72/21	6	British Liver Trust ¹²

α₁ AT, antitrypsin deficiency; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AICAH, autoimmune chronic active hepatitis; AST, aspartate transaminase; GGT, γ-glutamyl transpeptidase; GH, genetic haemochromatosis; HBV, hepatitis B virus infection; HCV, hepatitis C virus infection; PBC, primary biliary cirrhosis

- Mild rises (<3 ULN) justify interval retesting.
- Rises >5 ULN justify consideration of ultrasound if the cause is not apparent.

GGT is found in hepatocytes and in biliary epithelial cells. Its main use is in the diagnosis of biliary tract disease, in combination with ALP. It is widely and incorrectly regarded as a sensitive and specific marker of alcohol misuse.

The same statistical considerations apply to transaminases as to ALP, bilirubin and transaminases. Likewise, the actions to take in patients with risk factors for, or clinical evidence of, liver disease are the same, from the same documents. Some evidence, however, suggests that the yield from investigating raised GGT may be different from that for ALT or AST. The myth that a raised GGT is sensitive and specific for alcohol excess persists despite considerable evidence to the contrary. Studies have shown that the sensitivity of raised GGT for alcohol varies between 52% and 94%,⁴³⁻⁴⁴ depending on the population under study. Evidence also shows that the reference range for GGT is misleading; if a true reference range is established in non-drinkers, ULN values of 45 for men and 35 for women are obtained.⁴⁵ In a group with moderate alcohol intake, the levels rise to 66 and 40, respectively.

Hepatic fibrosis is present in only 11% of cases of asymptomatic patients with a raised GGT alone who do not drink excessively.⁴⁶ By contrast, patients drinking excess alcohol who have an isolated raised GGT rarely had considerable liver damage.⁴⁷

The same reviews that handled transaminases, ALP and bilirubin cite the primary purpose of GGT assessment as the clarification of the likely origin of an isolated ALP,^{2 4 5 8 24} used as a second-line test. The British Columbian guidelines also stated that an isolated non-progressive rise in GGT seldom reflects considerable liver disease, and a second review² referred to raised GGT as a common reason for mistaken diagnosis of viral hepatitis or inappropriate referral for liver biopsy, which often shows no abnormality in cases of an isolated minor GGT rise.⁴⁶ This point also appears in a *Journal of Insurance Medicine* review, drawing the same conclusions as above and offering little support for the utility of isolated GGT levels for actuarial predictive purposes.⁶ Conversely, however, GGT is raised in 50% of cases of NAFLD.⁴⁸

Therefore, there seems to be limited enthusiasm in the same reviews, which recommend the investigation of other slightly raised liver enzymes for the use of GGT levels in isolation, and consensus emerges that its main use lies in the clarification of a raised ALP. Differences in practice exist between laboratories: some do not include GGT in a liver profile, reserving it for second-line use, whereas others do. As highlighted by Aranda-Michel and Sherman,² it is important that requesters recognise the limitations of this test.

When should I refer for secondary assessment and possible liver biopsy?

In the absence of clear guidance, we recommend:

- Laboratory results >2 ULN (unexplained by laboratory tests);
- Or following disease-specific protocols if laboratory results show an underlying cause, to stage disease where applicable.

For most patients with abnormal liver enzyme levels, the pattern is non-specific, commonly raised ALT, ALP and GGT. The only investigation likely to produce a diagnosis if the above investigations are normal is liver biopsy.

The pathological effects of alcohol, drugs and the non-alcoholic fatty liver variants can only be diagnosed on liver biopsy. Percutaneous liver biopsy does, however, entail a

finite risk, primarily of haemorrhage, and the decision to offer liver biopsy is therefore a balance between the potential benefits of a treatable diagnosis to prevent hepatic fibrosis and risk. This benefit is clear in conditions such as autoimmune hepatitis but less so in conditions such as alcoholic liver injury. Conditions with a specific treatment that can change the natural history of the liver injury are found in between 7% and 18% of patients undergoing biopsy for abnormal liver enzymes.

Transaminase of twice the ULN are only associated with a histologically normal liver in around 6% of cases.³⁷ The most common diagnosis made on liver biopsy in this setting is either NAFLD or non-alcoholic steatohepatitis³⁷ (table 3). This diagnostic group accounts for two thirds of unexplained increase in liver enzymes. As above, however, clinical intervention data lacking the merits of liver biopsy in these situations are uncertain. Other important diagnoses include conditions such as antimitochondrial antibody-negative primary biliary cirrhosis and autoimmune hepatitis. A marked fibrosis on biopsy is common (table 2). An isolated mild, isolated, non-progressive rise in GGT is often not linked to liver disease and is rarely a reason for liver biopsy.

GMS contract indicator: None.

LITHIUM SAFETY MONITORING (WSAS, IDW)

Guidelines for safety monitoring in patients receiving lithium do not differ greatly qualitatively although a few differences in testing intervals are found. Several publications are available, indicating that management of this patient group often does not comply with published guidelines, and in view of the low toxicity threshold and potential severity of toxicity, there would seem to be a need for initiatives to improve monitoring.

When should I measure blood lithium concentrations and what additional testing is recommended?

We recommend:

- Testing at 3-month intervals;
- Testing in any patient presenting with potential signs of lithium toxicity;
- Testing a sample taken at least 12 h after the previous lithium dose, if possible at the same time after the dose;
- Measurement of renal function annually and in conjunction with any unexplained rise in serum lithium concentration;
- Measurement of thyroid function once 6 months in the initial years of treatment, annually thereafter if stable;
- Separate advice should be sought for pregnant women.⁴⁹

Table 3 Findings on liver biopsy for unexplained abnormal liver enzyme increase in 354 patients³⁷

Final diagnosis	n (%)
Non-alcoholic steatohepatitis	120 (34)
Non-alcoholic fatty liver disease	115 (32)
Cryptogenic hepatitis	32 (9)
Drug-related damage	27 (7.6)
Normal liver	21 (5.9)
Alcohol	10 (2.8)
Autoimmune hepatitis	7 (1.9)
Granuloma/sarcoid	6 (1.7)
Primary biliary cirrhosis	5 (1.4)
Primary sclerosing cholangitis	4 (1.1)
Haemochromatosis	3 (0.9)
Secondary biliary cirrhosis	2 (0.6)
Amyloid	1 (0.3)
Glycogen storage disease	1 (0.3)

Although consensus-based rather than evidence-based, several guideline sources recommend routine monitoring of lithium in stable patients at intervals of 1–3 months,⁵⁰ 2 months,⁵¹ 3 months,^{52–54} 3–6 months^{55–56} or at least once in 6 months.^{57–58} Most guidance recommending intervals of more than 3 months advocates more frequent testing in certain situations or use the qualifier “at least”, and we consider the 3-month recommendation to be the most representative for the average patient. The 3-month interval also appears in several locally derived guidelines.^{52–59–60} Despite these, there is good evidence that medical systems and practices often result in inadequate monitoring.^{61–64} Lithium has also been a topic of several large medical negligence claims.⁶⁵ Lithium toxicity can produce death and long-term sequelae and can occur as a result of a wide range of factors including drug treatment, concomitant illness and age-related renal changes.⁶⁶ Monitoring has been shown to reduce the risk of toxicity.^{67–68} Shared care management has been proposed as a means of reconciling the greater compliance with monitoring guidelines reported in secondary care with the success of joint primary and secondary care in mental illness.^{62–69}

Guidelines on when a sample should be taken for lithium measurement (in the non-acute situation) vary slightly from at least 10 h to 12–18 h after the last dose. The *British National Formulary (BNF)* advocates 12 h,⁶² consistent with historical recommendations, based on the fact that lithium concentrations vary little between 12 and 24 h after a dose in healthy people.^{70–71} The 12-h recommendation would therefore seem simple and logical and appears in several other guidelines. As the half life of elimination of lithium in young patients with normal renal function may be only 8–10 h, it would also seem logical to keep as close as practicable to the same timing for successive samples to limit variability.⁵²

Although the guidance found does not refer to monitoring for the possible development of nephrogenic diabetes insipidus in long-term use, prescribers should be aware of this possibility in any patients presenting with polyuria.

When should I measure blood lithium concentrations after a change in dose or after starting treatment?

We recommend:

- Remeasurement after 3–4 days but within 1 week after changing a dose.

As the half life of elimination of lithium is approximately 8–40 h in human beings depending on age and renal function, steady-state conditions would be expected between 2 and 8 days after starting or increasing a dose.⁶² The same review of lithium prescribed advocates retesting after 1 week. This is consistent with the known pharmacokinetics of lithium and should allow the steady state to have been reached in most people, but similarly highlight the risk of accumulation in those in which the half life of lithium is prolonged.

Few consensus recommendations exist on retesting policies after a dose change, although we advocate rechecking if doses are changed as a result of a trend of low or high results but do not stipulate a retesting interval.⁵⁹ Although not evidence-based, this would seem prudent in view of the serious consequences of overdosage or underdosage and the narrow therapeutic margin. Where minor dose titrations are being made, it would seem reasonable to recommend a period of 3–4 days after changing a dose in most patients, as the steady state is likely to have been reached in patients with normal renal function, noting that, in elderly people or those with impaired renal function, a further check may be required to ensure that the steady state has been reached, particularly as the time taken to reach the steady state will

increase with increasing half life, as seen in renal impairment. This would also allow earlier detection of accumulation in patients with renal dysfunction or in elderly people, rather than waiting for a potentially toxic steady-state concentration to be reached.

What is the target range for lithium and what action should I take for raised lithium concentration?

We recommend:

- 0.6–1.0 mmol/l for most adult, non-elderly patients;
- 0.4–0.8 mmol/l for most elderly patients;
- patients managed specifically outside of these ranges (normally not exceeding 1.2 mmol/l) should be individually identified and the reason for the decision clearly documented in patient records.

It is important to understand that a therapeutic range offers a guide to efficacy and potential toxicity, but is not an unequivocal target range, which must necessarily be achieved in all patients for reasons of physiological variability.

Lithium has a narrow therapeutic margin between efficacy and toxicity. Different target ranges have been proposed, although most people acknowledge the need for some flexibility in their interpretation. These vary within the extremes of 0.4–1.2 mmol/l. The range cited in the *BNF* is 0.4–1.0 mmol/l as compared with 0.4–1.2 for the American Psychiatric Association⁷². Values <0.6 mmol/l have, however, been reported to be associated with poorer functioning and higher relapse rates in adults,^{73–74} and it is probable that the lower target ranges of 0.4–0.6 mmol/l will be used more in elderly people, in whom standard maintenance concentrations of 0.4–0.8 are reported.⁷⁵

However, these differences are of limited importance if the spirit of the guidance is correctly followed. Most point out that some patients may require concentrations slightly in excess of the more conservative ranges to achieve clinical stability, and conversely, some, particularly elderly, patients may be adequately controlled on doses below some ranges. This point is succinctly reviewed in the UK GMS Contract Quality and Outcomes framework guidance notes (target range cited 0.6–1.0, but qualified as above).⁷⁶ Although a narrower target range is proposed in the UK GMS contract, the accompanying guidance acknowledges the need for this flexibility.

As the main purpose of monitoring in this case is to avoid potential toxicity (ie trigger interval retesting or a change in dose) while ensuring a sufficient dose to maintain clinical stability, the range cited in the *BNF* would seem, albeit not on evidence-based findings, to offer a satisfactory balance between the need to predict toxicity and recognise the relatively wide range of doses required in clinical practice.

It follows from this that patients in whom a clinical decision has been made to maintain lithium concentrations outside of a target range should be clearly documented as such to avoid inappropriate change in dose by another practitioner.

The value of 1.5 is cited as a level at which the incidence of adverse events rises considerably,⁷⁷ and as a threshold for at least temporarily stopping treatment. In view of this, it would not seem prudent to include higher values (eg >1.0 mmol/l) within the usual range.

GMS contract indicator: percentages of patients on lithium treatment with:

- A record of lithium level checked in the preceding 6 months;
- A record of serum creatinine and thyroid stimulating hormone checked in the preceding 15 months;

- A record of lithium levels within the therapeutic range in the preceding 15 months (range cited as normal 0.6–1.0 mmol/l).

D-DIMER TESTING AND DEEP VENOUS THROMBOSIS OR PULMONARY EMBOLISM (MJG, ACW)

The guidance mentioned below is taken largely from the British Committee for Standards in Haematology document: The diagnosis of deep vein thrombosis (DVT) in symptomatic outpatients and the potential for clinical assessment and D-dimer assays to reduce the need for diagnostic imaging.⁷⁸ This emphasises the need for testing, if carried out, to be combined with appropriate clinical assessment. Adoption of a suitable clinical scoring system should allow a standardised approach to primary (and secondary) care assessment of possible DVT.

In which patients with suspected DVT should a D-dimer test be carried out in a primary care setting?

We recommend:

- Testing patients with suspected DVT but Wells' probability score <2.
- Patients with higher probability scores should be referred for diagnostic imaging after a clinical algorithm depending on local service provision.

D-dimers are increased as a result of the degradation of fibrin, which may have formed as a result of a clot, but other situations giving rise to an increased fibrinogen will produce a high result. The use of this test allows a diagnosis of DVT to be excluded if the D-dimer result is low but a positive test does not confirm a DVT, which requires other investigations. Adoption of a suitable clinical scoring system—a combination of a D-dimer test and a pre-test probability or clinical probability score—can be used to eliminate the need for diagnostic imaging as long as the combination gives a negative predictive value of >98%.^{78–81} The criteria listed by Wells⁸¹ are shown in figure 4. D-dimers are of limited positive predictive value but can be used in clinical algorithms to exclude venous thrombosis. There are numerous causes of raised D-dimers, which should be excluded before asking for the test (see below).

Which test?

Many different D-dimer tests are available and the aim should be to use a test with a high negative predictive value.⁸¹ The results from the test should be used with a probability score and not in isolation. The test should be carried out by, or in conjunction with, an accredited laboratory with satisfactory quality assurance.⁸² Cut-off values will vary depending on the method used and if possible should be audited locally. Old samples may give false-positive results with some methods.

Who to investigate?

D-dimers and probability scoring can be used to exclude DVT in patients presenting with clinical symptoms suggestive of a DVT as long as symptoms have been present for <14 days.⁸¹ Anyone who has already received heparin is excluded from this guidance,^{78–81} as are patients likely to have raised D-dimers secondary to other conditions including the following:

- Pyrexial
- Grossly unwell
- Bedridden
- Obviously infected/septic
- Recent surgery

- Known malignancy
- Inflammatory disease
- Liver failure
- Renal failure
- Cardiac failure
- Pregnant.⁷⁸

D-dimers may be raised in these situations, even in the absence of thrombosis. To avoid confusion, it would therefore seem appropriate to request imaging in these situations to establish whether the patient has a DVT or pulmonary embolism.

Post-test assessment

In patients with a low clinical probability score and a negative D-dimer, DVT can be excluded^{78–81} and no further investigation is required. Those patients with an unlikely clinical score in whom the D-dimer is positive or those patients classified as likely to have a thrombosis will require further investigation. Heparin should be given unless there is immediate access to diagnostic imaging,⁷⁸ hence a sample for D-dimers must be taken at this point if it is to be used in the clinical algorithm.

Compression ultrasound imaging is usually the main diagnostic tool used, although distal venous thrombosis can be missed. In high-risk patients rescans may be indicated to exclude any progression of a previously missed distal thrombosis. The risk of embolic events from a distal thrombus that does not progress is extremely low.⁷⁸

Clinical algorithm

A clinical algorithm needs to be designed according to resources and the local patient population. Many will already exist in the secondary care setting and require little modification for use in primary care or out-of-hours settings. One way these can vary is by changing the order in which tests are carried out. As long as the basic evidence-based principles are applied it should be possible to establish an algorithm suitable for the local clinical service provision.

Patients with a positive ultrasound should be fully anticoagulated initially with low-molecular-weight heparin followed by warfarin according to current guidelines.^{83–84} No other diagnostic investigations are required; however, consideration as to the cause of the thrombosis is essential, including the exclusion of underlying malignancy. Patients with DVT require full medical assessment. Thrombophilia

Table 4 Wells' criteria for likelihood estimation of lower extremity deep venous thrombosis⁸¹

Clinical characteristic	Score
Active cancer (patient receiving treatment for cancer in the previous 6 months or currently receiving palliative treatment)	1
Paralysis, paresis or recent plaster immobilisation of the lower extremities	1
Recently bedridden for ≥3 days, or major surgery within the previous 12 weeks requiring general or regional anaesthesia	1
Localised tenderness along the distribution of the deep venous system	1
Entire leg swollen	1
Calf swelling at least 3 cm larger than that on the asymptomatic side (measured 10 cm below tibial tuberosity)	1
Pitting oedema confined to the symptomatic leg	1
Previously documented deep vein thrombosis	1
Alternative diagnosis at least as likely as deep vein thrombosis	–2

A score of <2 is considered low probability for deep venous thrombosis.

Figure 1 Proposed algorithm for patients with an intermediate or high probability of a deep venous thrombosis (adapted from Wells *et al*⁸¹).

screening may be recommended after anticoagulation is completed.⁸⁵

One possible approach derived below (fig 1) is suggested from a previously published algorithm.⁸¹

GMS contract indicator: None.

CONCLUSION

This fifth review brings to a running total 66 question-answer sets written to provide an overview of current advice in use of laboratory tests in primary care. Answers to the first four question-answer sets can be found in Smellie *et al*.^{86–89} They have all used a common search method,⁹⁰ although where recent systematic reviews have been carried out, the guidance also relies heavily on the findings of these reviews. For authors wishing to consult the UK GMS Contract⁹¹ and related Quality and Outcomes framework⁷⁶ guidance, these can be found on their respective websites.

ACKNOWLEDGEMENTS

We thank Mrs Susan Richardson for typing this manuscript, Mrs G C Smellie for help in collating answers into this article and to the following people who reviewed the work: Professor I S Young, Dr D Housley (Association of Clinical Biochemists), Professor R Gama (Association of Clinical Pathologists), Dr E Logan (British Society for Haematology), Dr R Neal, Dr N Campbell (Royal College of General Practitioners), Dr D Gozzard, Dr D Freedman (Royal College of Pathologists), and other Council members of these Associations and Colleges who have assisted in recruiting reviewers.

This work has been supported (in alphabetical order) by the Association of Clinical Biochemists*, Association of Clinical Pathologists*, Association of Medical Microbiologists, British Society for Haematology, Royal College of General Practitioners, Royal College of Pathologists* and the Sowerby Centre for Health Informatics in Newcastle (SCHIN), representatives of which have contributed to the reviewing process. The opinions stated are, however, those of the authors.

* These organisations contributed direct funding to support the project start up.

Authors' affiliations

W S A Smellie, Department of Chemical Pathology, Bishop Auckland General Hospital, Durham, UK
J Forth, Sowerby Centre for Health Informatics, Bede House, All Saints Business Centre, Newcastle upon Tyne, UK
S Ryder, Department of Gastroenterology, Queen's Medical Centre, Nottingham, UK
M J Galloway, Department of Haematology, City Hospitals Sunderland NHS Trust, Sunderland Royal Hospital, Sunderland, UK
A C Wood, Department of Haematology, James Cook University Hospital, Teesside, UK
I D Watson, Department of Clinical Biochemistry, University Hospital Aintree Liverpool, UK

Competing interests: None declared.

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