

LIVER FUNCTION TESTING
in primary care
QUIZ Feedback



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EXPERT SUMMARY

Liver function tests comprise several different laboratory parameters, none of which is either 100% sensitive or specific for liver disease. Although various combinations reflect patterns of liver disease, overlap may occur – e.g. liver infiltration, drug-induced cholestasis, biliary obstruction.

It is therefore important to consider the LFT results in the clinical context – does the patient have symptoms or signs suggestive of disseminated malignancy, cholangitis, what is the drug history, what does the abdominal ultrasound demonstrate?

The most confusion surrounds monitoring guidelines for drug-induced hepatotoxicity. Most hepatotoxicities are idiosyncratic. In a recent update at the American Liver Meeting, Professor Willis Maddrey stated that routine monitoring of LFTs in patients on statins was not required. Rather, patients should be asked about any new symptoms of hepatitis both nonspecific (nausea, anorexia, malaise, fatigue, RUQ discomfort) and specific (itching, dark urine/pale stools, jaundice). If symptoms are associated with liver dysfunction then the agent should be stopped and the LFTs monitored closely. If patient is jaundiced (bilirubin >2xULN) then the patient should be referred to secondary care.

Also, several studies have not demonstrated an increased risk for hepatotoxicity in patients with underlying chronic liver disease (e.g. HCV, NAFLD)

Associate Professor Ed Gane

We are sorry you did not return a quiz to us. These questions were designed to represent a range of situations where investigation of liver function may be required.

Please let us know if there is any way we can make our case studies more useful to you because we want our resources to be helpful for your day-to-day practice. We would be pleased to receive any suggestions that you have.

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QUIZ: LIVER FUNCTION TESTING IN PRIMARY CARE

- A 52 year-old man has been on statins for the previous 3 years, and remains well. Select the most appropriate option for routine LFT monitoring.

No routine monitoring of liver function

Six monthly ALT only

Six monthly LFT panel

Yearly ALT only

Yearly LFT panel
- A 47 year-old woman presents with jaundice, RUQ pain and fever. LFTs reveal both AST and ALT >1200 IU/L. What laboratory tests would you request?

Anti-HCV Anti-HBs

HBsAg Anti-HAV IgM
- An 18 year-old man visited the after hours surgery with a sore throat. His blood test results have been forwarded to you. Blood film shows lymphocytosis with 60% atypical forms, and he has a positive screening test for glandular fever. The liver function tests show mild-moderate elevations in the transaminases. Select the most appropriate option for follow up liver function testing.

Check in about 3 months

Do not check LFTs

Only test if clinical symptoms worsen

Test regularly until clinical symptoms improve

Test when clinical symptoms improve

Comment.....
- A 33 year-old man had LFTs performed as part of an insurance medical 3 months ago. The ALT was noted to be slightly elevated at 63 (reference range 0 – 45 IU/L), and a recent check reveals it is still elevated. After reviewing the history and performing an examination, you determine the man was involved with injecting drugs in his late teens. Select the test(s) you would perform.

Anti-HCV Anti-HBs

HBsAg Anti-HAV
- 24 year-old woman was diagnosed with Gilbert's disease after presenting with mild jaundice after taking part in the 40-hour famine. Investigations revealed mild unconjugated hyperbilirubinaemia. Her mother had the same disorder. During her first pregnancy, she is concerned high bilirubin levels will harm her baby, and requests regular bilirubin tests throughout her pregnancy. What do you recommend?

Baseline bilirubin

Full LFT panel

Monthly bilirubin tests

No checks of bilirubin
- A 20 year-old Maori woman presents for a routine smear appointment. You note her hepatitis status is not recorded and she has not been immunised against hepatitis. Other than ethnicity, she has no risk factors. How would you follow this up?

Check at a later date

Only test if signs and symptoms of hepatitis

Request HBsAg

Request anti-HBs
- What is the probability of an adult with acute hepatitis B progressing to chronic hepatitis B infection?

< 5% 5–10%

10–15% 15–20%

20–25%
- Indicate the set of results that most likely indicate a hepatocellular pattern.

A B C D
- Indicate the set of results that most likely indicate a cholestatic pattern.

A B C D
- Indicate the set of results that most likely indicate a mixed pattern.

A B C D

Table 1: Indicate the set of results below that most likely indicate a hepatocellular pattern

	Alk Phos (40-100 IU/L)	AST (0-45 IU/L)	ALT (0-45 IU/L)	GGT (0-60 IU/L)	Bilirubin (0-20 µmol/L)	T. protein (60-84 g/L)	Albumin (35-48 g/L)
A	35	68	62	53	18	70	36
B	24	32	28	75	14	68	37
C	150	42	33	80	32	63	35
D	305	432	398	273	67	72	38

Table 2: Indicate the set of results below that most likely indicate a cholestatic pattern

	Alk Phos (40-100 IU/L)	AST (0-45 IU/L)	ALT (0-45 IU/L)	GGT (0-60 IU/L)	Bilirubin (0-20 µmol/L)	T. protein (60-84 g/L)	Albumin (35-48 g/L)
A	98	48	52	42	24	78	44
B	104	270	230	62	19	63	36
C	24	44	34	29	18	127	44
D	130	43	44	104	32	83	45

Table 3: Indicate the set of results below that most likely indicate a mixed pattern

	Alk Phos (40-100 IU/L)	AST (0-45 IU/L)	ALT (0-45 IU/L)	GGT (0-60 IU/L)	Bilirubin (0-20 µmol/L)	T. protein (60-84 g/L)	Albumin (35-48 g/L)
A	198	43	31	98	20	70	37
B	85	42	37	120	28	64	36
C	83	77	74	59	21	69	40
D	130	264	228	140	32	79	44

QUIZ FEEDBACK:

Responses from Colleagues, GP Panel and Expert Review

1. A 52 year-old man has been on statins for the previous 3 years, and remains well. Select the most appropriate option for routine LFT monitoring.

	You	Your Peers	GP Panel
No routine monitoring of liver function		94 %	+
Six monthly ALT only		<1 %	
Six monthly LFT panel		1 %	
Yearly ALT only		2 %	
Yearly LFT panel		3 %	

GP Panel

The panel expected that the most GPs would be surprised at the change in recommendations around monitoring LFTs of people on statins. This change is expected to result in more patients benefiting from statin use. The previous requirement for monitoring of liver function may have put patients off statins because the need for testing implied a significant level of risk. We now know that risk is negligible.

People should not be denied the benefits of statins because of baseline abnormal LFTs and monitoring is of no benefit.

Expert Comment

A recent review of statins suggests that the incidence and severity of statin-induced hepatotoxicity has been overestimated. Whilst mild liver function test abnormalities may be observed in up to 15% of patients receiving statins, in most people this resolves spontaneously despite continued use.

Severe toxicity is associated with clinical symptoms. Therefore, patients receiving statins should be regularly asked about any new symptoms including nonspecific nausea, anorexia, malaise, fatigue, RUQ discomfort as well as specific itching or dark urine/pale stools (jaundice). If there is associated liver dysfunction then the agent should be stopped and the LFTs monitored closely. If the patient is jaundiced (bilirubin: > 2 times ULN) then the patient should be referred to secondary care.

Also, several studies have now observed that patients with underlying chronic liver disease (e.g. HCV, NAFLD) do not appear to be at increased risk for developing statin-induced hepatotoxicity.

2. A 47 year-old woman presents with jaundice, RUQ pain and fever. LFTs reveal both AST and ALT >1200 IU/L. What laboratory tests would you request?

	You	Your Peers	GP Panel
Anti-HCV		51 %	±
Anti-HBs		29 %	
HBsAg		88 %	+
Anti-HAV IgM		83 %	+

GP Panel

ALT and AST levels this elevated are highly suggestive of acute hepatitis. This is most likely to be hepatitis A or B. Most people with hepatitis C will not be symptomatic during the acute phase and cannot be reliably diagnosed in the acute phase because of the prolonged period of sero-conversion.

The best initial tests are HBsAg and Anti-HAV IgM. For patients at high risk of hepatitis C, people who inject street drugs, share needles or had a blood transfusion prior to 1992, the panel would also test anti-HCV antibodies.

Expert Comment

The most common cause of acute icteric hepatitis in New Zealand adults is still acute HBV infection. Europeans are at highest risk because of lack of natural immunity whilst most Polynesian and Asian New Zealanders are immune from childhood exposure. The most common route of transmission in adults is sexual transmission, from a partner with chronic HBV infection.

In an injecting drug user, the most likely cause of acute icteric hepatitis is acute HBV infection. The second most likely cause is acute HCV infection.

Acute HAV infection should also be considered if risk factors, for example MSM or recent travel to areas with endemic HAV – Indian subcontinent, Asia, Central and South America, Eastern Europe, Pacific Islands and Africa.

In adolescents, acute EBV infection should be considered.

3. **An 18 year-old man visited the after hours surgery with a sore throat. His blood test results have been forwarded to you. Blood film shows lymphocytosis with 60% atypical forms, and he has a positive screening test for glandular fever. The liver function tests show mild-moderate elevations in the transaminases. Select the most appropriate option for follow up liver function testing.**

	You	Your Peers	GP Panel
Check in about 3 months		18 %	
Do not check LFTs		38 %	±
Only test if clinical symptoms worsen		43 %	
Test regularly until clinical symptoms improve		3 %	
Test when clinical symptoms improve		3 %	

GP Panel

The spread of responses for this question indicates the difficulties that arise when LFTs are performed for someone with infectious mononucleosis. The panel felt that now abnormal results had been found, they would feel duty bound to follow them up. However, they would not routinely test LFTs of people with suspected infectious mononucleosis.

Expert Comment

Acute EBV hepatitis always resolves in immunocompetent individuals. However, because >90% of New Zealanders will develop acute EBV infection during adolescence, it is recommended that follow-up LFTs be checked after resolution of the EBV infection to exclude pre-existing chronic liver disease. Therefore, anyone noted to have abnormal LFTs during investigation for acute EBV infection should be followed (say 6 months later) to ensure that these normalise, as expected for acute EBV. If this does not occur, then appropriate investigations should be performed to identify other aetiologies such as inherited conditions, autoimmune diseases, or viral hepatitis.

4. A 33 year-old man had LFTs performed as part of an insurance medical 3 months ago. The ALT was noted to be slightly elevated at 63 (reference range 0 – 45 IU/L), and a recent check reveals it is still elevated. After reviewing the history and performing an examination, you determine the man was involved with injecting drugs in his late teens. Select the test(s) you would perform.

	You	Your Peers	GP Panel
Anti-HCV		97 %	+
Anti-HBs		34 %	
HBsAg		83 %	+
Anti-HAV		6 %	

GP Panel

The panel felt that this question was about testing for chronic hepatitis but pointed out that there may well be other causes for this persisting elevation in ALT level. For example: non-alcoholic liver disease, alcohol, drugs or haemochromatosis.

The ALT level is only slightly elevated but this is not an accurate marker of the significance of the liver disease.

The panel would test HBsAg and, given his drug injection history, anti-HCV. Hepatitis A does not become chronic and anti-HBs is a marker for immunity from a previous infection or immunisation.

Expert Comment

Almost 70% of people with a previous history of injecting drug use (IDU) will have chronic hepatitis C infection. Almost 95% of people with newly diagnosed HCV infection will have a past history of IDU. Often this history will be difficult to extract because of the stigma people associate with admitting IDU (often 20 or 30 years earlier). Note that almost 10% of those with chronic HCV infection have persistently normal LFTs – i.e. it is necessary to ask the question “have you ever injected drugs in the past” in order to identify all patients with chronic hepatitis C.

Alcohol abuse is an important factor to be considered in all patients with chronic hepatitis C, not only because of the increased prevalence in previous IDU but also because heavy alcohol use is associated with more rapid progression to HCV-cirrhosis. Recent studies have also demonstrated that heavy cannabis use (2 or more joints per day) is also associated with more rapid fibrosis progression.

All patients with chronic HCV infection should have their immune status to HAV and HBV checked and if not immune, they should be offered vaccination. Also, all patients with chronic HBV infection should have their immune status to HAV checked and if not immune should be offered HAV vaccination. This is because patients with chronic viral hepatitis have much higher mortality following acute superinfection with HAV or HBV than those without chronic viral hepatitis.

5. **24 year-old woman was diagnosed with Gilbert's disease after presenting with mild jaundice after taking part in the 40-hour famine. Investigations revealed mild unconjugated hyperbilirubinaemia. Her mother had the same disorder. During her first pregnancy, she is concerned high bilirubin levels will harm her baby, and requests regular bilirubin tests throughout her pregnancy. What do you recommend?**

	You	Your Peers	GP Panel
Baseline bilirubin		7 %	
Full LFT panel		2 %	
Monthly bilirubin tests		1 %	
No checks of bilirubin		91 %	+

GP Panel

The panel were concerned about reinforcing this woman's anxiety about her bilirubin levels by performing a test. It may seem an easy option to agree to her request but the results are likely to be elevated and requests for more tests will most likely follow. The woman may then start to associate test result levels with how she feels and become more anxious.

The panel would give firm reassurance that Gilbert's syndrome does not increase risks for her baby.

Expert Comment

Gilbert's Syndrome is an autosomal dominant condition, where a partial deficiency in bilirubin conjugation enzyme results in unconjugated hyperbilirubinaemia. Note that in certain cases, the total bilirubin may remain normal until subjected to certain conditions such as prolonged fasting, certain drugs (not pregnancy). This unconjugated hyperbilirubinaemia is harmless, even during pregnancy.

6. **A 20 year-old Maori woman presents for a routine smear appointment. You note her hepatitis status is not recorded and she has not been immunised against hepatitis. Other than ethnicity, she has no risk factors. How would you follow this up?**

	You	Your Peers	GP Panel
Check at a later date		< 1%	
Only test if signs and symptoms of hepatitis		3 %	
Request HBsAg		85 %	+
Request anti-HBs		35 %	

GP Panel

The panel pointed out that at 20 years of age this would be this young woman's first cervical smear, not a routine one. This is a time when the clinician has to negotiate many emotional and cultural issues, and developing a good rapport and relationship with the patient would be a priority. The panel acknowledged that raising the issue of hepatitis screening at this time would be difficult.

Never-the-less, it is worth considering the high risk of chronic hepatitis B in Māori, Pacific and Asian people from infections contracted in childhood. If the patient in the case study has chronic hepatitis B and the test is not done, the next time she may be seen, may well be when she has already transmitted hepatitis B to her baby. The baby then has a greater than 90% chance of progressing to chronic hepatitis.

Expert Comment

Both HBsAg and anti-HBs should be tested. If HBsAg is positive, then the patient should be followed by 6 monthly ALT and AFP. If either ALT or AFP become elevated then she should be referred to secondary care. The Hepatitis Foundation, (PO Box 647, Whakatane) are happy to facilitate this follow-up in partnership with the general practitioner.

If anti-HBs is positive, the patient is then immune and no follow-up is required.

If both HBsAg and anti-HBs are negative, then HBV vaccination should be offered.

Additional Note: this scenario of a 20 year old Maori with chronic HBV should not occur in 2007. Universal neonatal vaccination was introduced in 1987 therefore protecting all New Zealanders aged 20 years or younger. Exceptions are those born outside New Zealand in countries with endemic HBV – i.e. anywhere in the Asia-Pacific (although most countries have had active neonatal programmes over the last decade).

7. What is the probability of an adult with acute hepatitis B progressing to chronic hepatitis B infection?

	You	Your Peers	GP Panel
< 5%		93 %	+
5–10%		3 %	
10–15%		1 %	
15–20%		<1 %	
20–25%		1 %	

GP Panel

The difference in viral clearance rates between adults and children with acute hepatitis B is interesting.

In neonates infected from their mother's, over 90% do not clear the virus and are left with chronic hepatitis B.

In children, infected from other children, over 50% develop chronic hepatitis.

In adults, less than 5% develop chronic hepatitis.

Expert Comment

The older the patient at the time of exposure, the more likely he/she is to spontaneously eradicate the infection. This reflects a mature anti-HBV immune response. The downside is that this is usually associated with acute icteric hepatitis and in 1% of cases, acute liver failure. In contrast, jaundice is rare in children who usually develop persistent infection

Why age determines outcome of acute infection is unknown. It is interesting to note that the reverse is true of vaccine responsiveness. >98% of neonates will develop a protective response, whilst only 90% of 20 year olds and 80% of those aged over 40 years.

8. Indicate the set of results that most likely indicate a hepatocellular pattern

	Alk Phos (40-100 IU/L)	AST (0-45 IU/L)	ALT (0-45 IU/L)	GGT (0-60 IU/L)	Bilirubin (0-20 µmol/L)	T. protein (60-84 g/L)	Albumin (35-48 g/L)
A	35	68	62	53	18	70	36
B	24	32	28	75	14	68	37
C	150	42	33	80	32	63	35
D	305	432	398	273	67	72	38

	You	Your Peers	GP Panel
A		67 %	+
B		<1 %	
C		1 %	
D		31 %	

GP Panel

- A. Hepatocellular pattern, with raised AST and ALT. Possible causes: viral infection, NAFLD.
- B. Mild elevation of GGT only. Possible causes: excessive alcohol intake (non specific marker), phenytoin.
- C. Cholestatic pattern, with raised Alk Phos, bilirubin and GGT. Possible causes: gall stones, abdominal masses.
- D. Mixed pattern; with raises across all test parameters.

Expert Comment

Agree.
Both A and D may reflect hepatitis.

9. Indicate the set of results that most likely indicate a cholestatic pattern

	Alk Phos (40-100 IU/L)	AST (0-45 IU/L)	ALT (0-45 IU/L)	GGT (0-60 IU/L)	Bilirubin (0-20 µmol/L)	T. protein (60-84 g/L)	Albumin (35-48 g/L)
A	98	48	52	42	24	78	44
B	104	270	230	62	19	63	36
C	24	44	34	29	18	127	44
D	130	43	44	104	32	83	45

	You	Your Peers	GP Panel
A		1 %	
B		2 %	
C		2 %	
D		95 %	+

GP Panel

- A. Isolated bilirubin elevation. Most likely Gilbert's syndrome if most of the bilirubin is unconjugated.
- B. Predominantly hepatocellular pattern, Possible causes: viral infection, NAFLD.
- C. Raised total protein, consider causes of increased globulin fraction e.g. multiple myeloma, other causes of increased globulin.
- D. Cholestatic pattern. Possible causes: gall stones, abdominal masses.

Expert Comment

Agree – also consider infiltration (malignancy, amyloid, sarcoid).

Abdominal ultrasound should be considered

10. Indicate the set of results, that most likely indicate a mixed pattern

	Alk Phos (40-100 IU/L)	AST (0-45 IU/L)	ALT (0-45 IU/L)	GGT (0-60 IU/L)	Bilirubin (0-20 µmol/L)	T. protein (60-84 g/L)	Albumin (35-48 g/L)
A	198	43	31	98	20	70	37
B	85	42	37	120	28	64	36
C	83	77	74	59	21	69	40
D	130	264	228	140	32	79	44

	You	Your Peers	GP Panel
A		1 %	
B		1 %	
C		1 %	
D		97 %	+

GP Panel

- A. Predominantly cholestatic pattern; elevated Alk Phos supported by elevated GGT.
- B. Predominantly cholestatic, elevated GGT and bilirubin.
- C. Hepatocellular pattern.
- D. Mixed pattern.



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