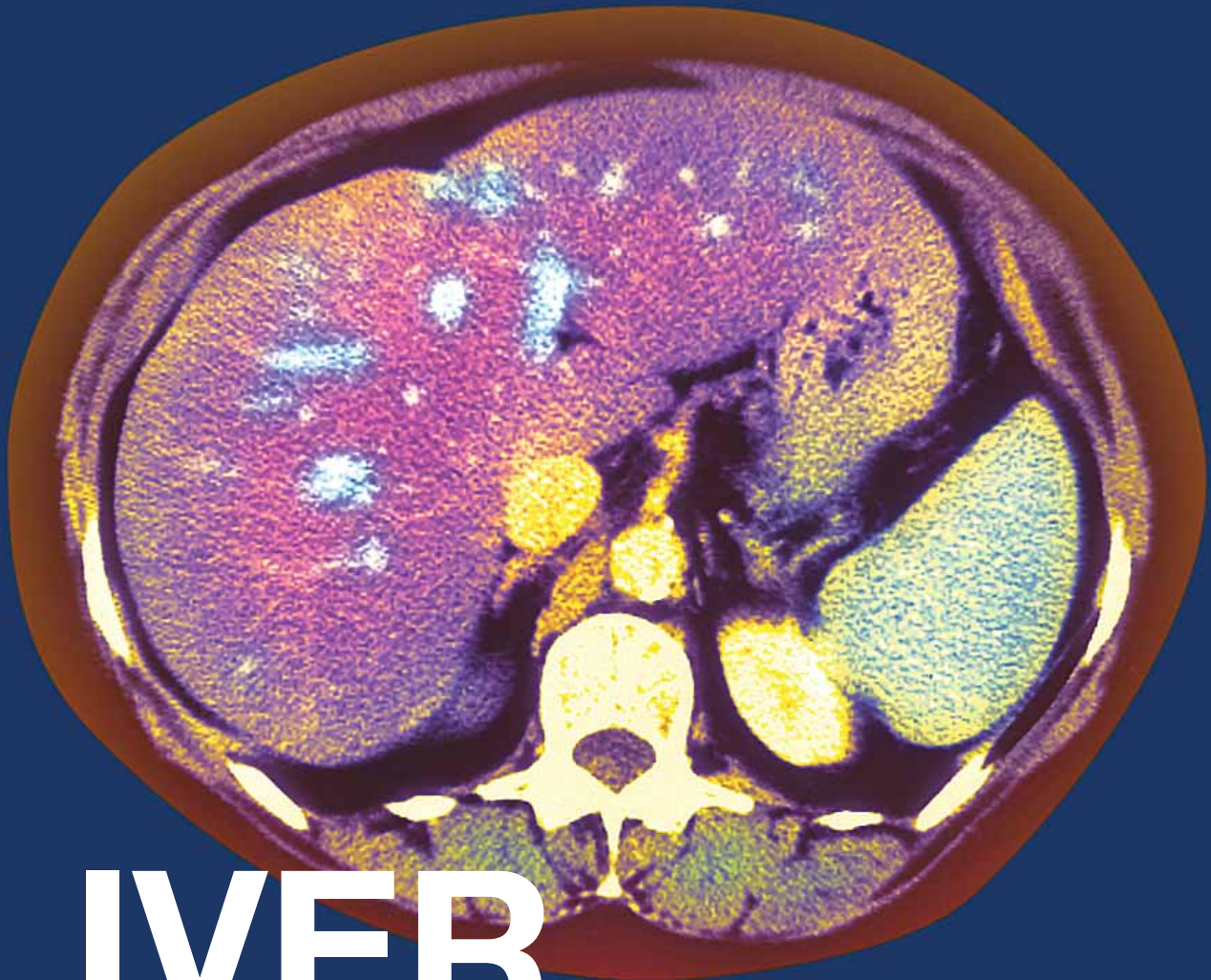


# CSP

## Common Sense Pathology

A REGULAR CASE-BASED SERIES ON PRACTICAL PATHOLOGY FOR GPs



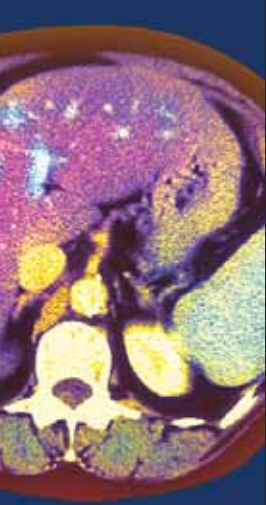
# LIVER

## function tests

A JOINT INITIATIVE OF



Australian  
**Doctor.**



## Liver function tests



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### Introduction

Raised liver enzymes are a common finding in clinical practice. Indeed, liver enzymes are elevated in 1-4% of asymptomatic patients.<sup>1</sup> The pattern of liver enzyme elevation is rarely characteristic for a particular disease state, and needs to be interpreted together with the clinical findings. Guidelines are based on expert opinion as there is almost no direct clinical study evidence on this topic. The general consensus, however, is that classifying liver enzyme elevation as due to either hepatocellular damage or cholestasis can be helpful in directing the next appropriate investigations.

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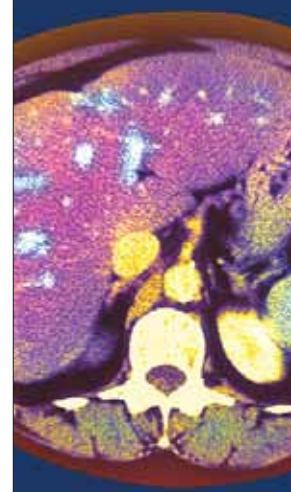
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## Case 1

A 42-year-old woman had liver function measured during a routine visit as follows:

Albumin	38g/L	(34-48g/L)
Protein	70g/L	(65-85g/L)
Total bilirubin	10µmol/L	(6-24µmol/L)
Gamma glutamyl transferase (GGT)	82U/L	(0-60U/L)
Alkaline phosphatase (ALP)	106U/L	(30-110U/L)
Alanine aminotransferase (ALT)	71U/L	(0-55U/L)
Aspartate aminotransferase (AST)	63U/L	(0-45U/L)
Lactate dehydrogenase (LD)	264U/L	(110-230U/L)

She had type 2 diabetes which was controlled on diet, with a HbA<sub>1c</sub> of 7.1%. Her waist circumference was 92cm and body mass index was 29kg/m<sup>2</sup>. She drank no alcohol. Her plasma lipids showed a mild elevation of triglycerides. Her liver function tests had shown similar abnormalities for the past three years.

### Questions:

1. What are the potential causes of liver enzyme elevation in this patient?
2. What further investigation is appropriate?
3. What constitutes a significant change in liver enzymes?

This patient has a mild elevation in transaminases (aspartate aminotransferase [AST] and alanine aminotransferase [ALT]) and gamma glutamyl transferase (GGT).

ALT is located in hepatic cytoplasm, and liver AST is found in two forms, one located in the hepatocellular cytoplasm and the other in the mitochondria. Increased transaminases therefore indicate liver cell damage. Raised GGT is a non-specific finding, and may be due to enzyme induction rather than liver disease.

It is appropriate to look for treatable causes of liver cell damage with this pattern of liver enzyme elevation, particularly infectious hepatitis and iron

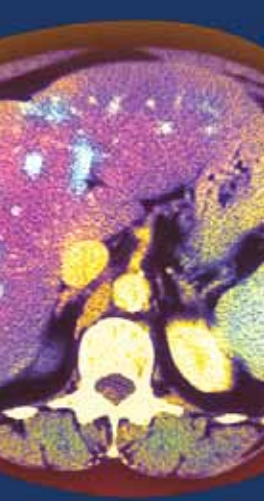
overload. Some other common causes are listed in Table 1. Hepatitis C is found in up to 3% of the population<sup>2</sup> and hepatitis B surface antigen is positive in 0.1-2%.<sup>1</sup>

In Australia, hereditary haemochromatosis is almost always associated with homozygous status for the C282Y mutation in the HFE gene, with a homozygote prevalence of about 1 in 250. However, in a recent study of C282Y homozygotes, only 28% of men and 1.2% of women were iron overloaded.<sup>3</sup> Thus transferrin saturation is still the most appropriate screen for iron overload.

There is no laboratory test which can reliably detect alcohol abuse. Alcohol and drug use, including over-the-counter and herbal medicines, needs to be enquired for carefully. An increased AST:ALT ratio of over two, or other laboratory findings seen in alcohol abuse such as macrocytosis, may confirm the clinical impression but are not always present, and may be seen in other causes of liver disease. Very rarely, other treatable chronic liver disease may be detected on biochemical testing, for example autoimmune hepatitis, alpha-1 antitrypsin deficiency or Wilson's disease.

However, after exclusion of treatable disease, by far the most common cause of mildly (up to five times above normal) elevated transaminases in Western patients is fatty liver. Inflammation is a commonly associated feature. The prevalence of fatty liver ranges from 3% to 20%.<sup>4</sup> Most patients are asymptomatic or have non-specific symptoms of fatigue or bloating; and more than 10% have normal enzyme levels.<sup>4</sup> An ultrasound in this patient showed typical features of a bright hyper-echoic texture.

In hepatosteatosis, deposition of macroscopic fat vesicles in the liver is associated with hypertriglyceridaemia and insulin resistance. Overweight and obesity increase the risk of disease up to six times<sup>3</sup> although many patients are of normal weight. Other risk factors include diabetes or metabolic syndrome, very rapid weight loss and medication including corticosteroids, tamoxifen, amiodarone and diltiazem. It is rare for fatty liver to progress to steatohepatitis or fibrosis, but it is serious if it does. Up to 50% of patients with biopsy-proven steatohepatitis will progress to fibrosis and around 15% will progress to cirrhosis. Unfortunately, there



**Table 1. Common causes of hepatocellular damage or cholestasis**

<b>Hepatocellular damage (predominant ALT elevation)</b>	<b>Cholestasis (predominant ALP elevation)</b>
Infections (includes hepatitis B, C and A, Epstein-Barr virus, cytomegalovirus)	Biliary obstruction
Fatty liver (including alcohol)	Medication (see Table 2)
Haemochromatosis	Intrahepatic (eg, metastases)
Medication induced (eg, paracetamol, methotrexate, cytotoxics)	Pregnancy associated

is no consensus on when liver biopsy might be appropriate, given the usually benign prognosis and lack of effective therapy. While no medication has been shown to reduce liver fat content, exercise and weight loss of at least 10% has been shown to improve liver enzymes, presumably by reducing insulin resistance.<sup>5</sup> It is also reasonable to stop any medications which may be contributing.

What monitoring is appropriate, and what constitutes a significant change in enzymes, is another common question. This needs to be considered in light of the patient's overall condition; more frequent monitoring is needed in a clinically unwell patient or where an acute or evolving disease process is suspected.

In an asymptomatic patient with mildly elevated transaminases, the most cost-effective approach is to retest 2-3 weeks later, rather than immediately embarking on other serological tests or imaging studies.<sup>1</sup> Mild liver enzyme elevations often do not

persist. The best natural history data come from 1864 patients from the NHANES III study, who had liver function tests repeated 18 days after the initial evaluation. If the first test was abnormal, the second test was also abnormal in only a third of cases. Conversely, if the first test was normal, the second test was abnormal in fewer than 5% of subjects.<sup>2</sup>

This study also determined the coefficient of variation of liver enzyme levels within individuals. This was highest for bilirubin at 23%, followed by ALT at 20%, GGT at 14% and alkaline phosphatase (ALP) at 6.5%. To be 99% certain a repeat test differs from a previous result, it needs to be more than twice the intra-individual coefficient of variation for that test. This "least significant change" is therefore about 45% for bilirubin, 40% for ALT, and so on. So in the context of the patient in Case 1 with an initial ALT of 71U/L, a repeat result would need to be less than 43U/L or greater than 99U/L to be significantly different from the first.

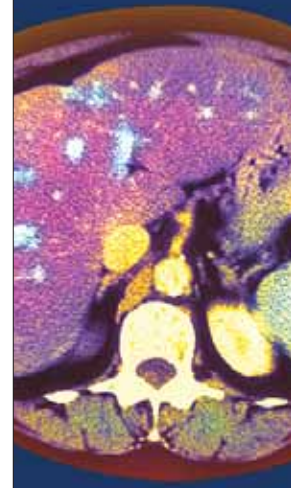
It is also worth noting that reference intervals for liver enzymes often vary between laboratories, usually reflecting the population used to establish the limits rather than the assay in use. This adds to the complexity of interpreting liver function tests when results from more than one laboratory are being used. However, inter-laboratory variation is relatively small compared with the large variability within individuals.

## Case 2

A 17-year-old boy had been unwell for one week with fever, malaise and cervical lymphadenopathy. Liver function tests and complete blood picture were as follows:

**Table 2. Commonly used medications associated with increased ALP or bilirubin**

Allopurinol
Amoxicillin/clavulanic acid
Captopril
Carbamazepine (enzyme induction)
Erythromycin
Flucloxacillin
Gold salts
Oestrogen (includes contraceptive pill)
Phenytoin (enzyme induction)
Testosterone
Trimethoprim/sulphamethoxazole



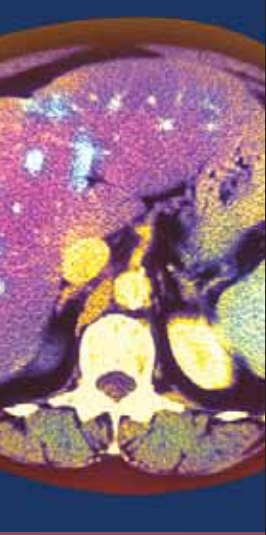
Albumin	40g/L	(34-48g/L)	Haemoglobin	152g/L	(115-155g/L)
Protein	80g/L	(65-85g/L)			
Total bilirubin	31µmol/L	(6-24µmol/L)	Platelets	186x10 <sup>9</sup> /L	(150-450x10 <sup>9</sup> /L)
GGT	382U/L	(0-60U/L)			
ALP	390U/L	(30-110U/L)	White cell count	17.0x10 <sup>9</sup> /L	(4.0-11.0x10 <sup>9</sup> /L)
ALT	528U/L	(0-55U/L)	Neutrophils	21.0%	
AST	316U/L	(0-45U/L)	Lymphocytes	79.0%	reactive

**Questions:**

**1. What further tests are appropriate to establish the diagnosis?**

In this patient, as in Case 1, the predominantly raised ALT compared with ALP suggests liver cell damage. This is one of the few characteristic patterns for liver enzyme elevation. The main clue is the raised reactive lymphocyte count. IgM for Epstein-Barr virus was raised in this patient, con-

firmed acute infection. The age of the patient is typical, as most acute infections occur in adolescents. In addition, lactate dehydrogenase (LD) in this patient was significantly elevated, to a higher degree than ALT, at 757U/L (reference range [RR] 110-230U/L), another typical finding. About one-third of infected patients will develop raised liver enzymes. The raised LD probably reflects increased lymphocyte turnover, but in up to one



in six patients, haemolysis will also occur (either autoimmune or associated with hypersplenism), leading to an increase in unconjugated bilirubin as seen in this patient.

The natural history of acute infectious mononucleosis is almost always benign. In a prospective study of 150 American patients with acute Epstein-Barr virus infection, all laboratory abnormalities had resolved within a month.<sup>6</sup> In this patient, ALT had fallen from 528U/L to 75U/L (RR 0-55U/L), and bilirubin had normalised, within 11 days.

### Case 3

A 66-year-old man presented with weight loss and anaemia. His liver function tests were as follows:

Albumin	22g/L	(34-48g/L)
Protein	59g/L	(65-85g/L)
Total bilirubin	12µmol/L	(6-24µmol/L)
GGT	926U/L	(0-60U/L)
ALP	527U/L	(30-110U/L)
ALT	104U/L	(0-55U/L)
AST	96U/L	(0-45U/L)
LD	246U/L	(110-230U/L)

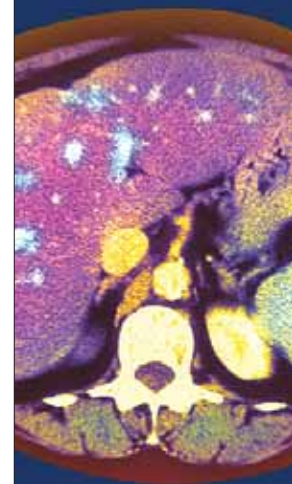
### Questions:

1. What is the likely diagnosis?
2. What further tests are appropriate?

In Case 3, the predominant abnormality is elevated ALP and GGT, with a lesser increase in ALT. This pattern suggests cholestasis. Some common causes are listed in Table 1. GGT and ALP are normally present at the hepatocyte cell membrane, particularly on the canalicular surface where bile is transported. In cholestasis, bile acids accumulate and dissolve fragments of cell membrane, releasing bound enzymes into the bloodstream.

Cholestasis can be further classified as being due to biliary obstruction (extrahepatic), or functional impairment in bile formation (intrahepatic). Elevated ALP and GGT may also be seen in enzyme induction by alcohol or medication (although usually stable and only up to twice the upper limit of normal). The elevated GGT in this patient makes it more likely that ALP is of hepatic origin. If this is in doubt, particularly if ALP is raised in isolation, electrophoresis may be necessary to exclude other causes of raised ALP, including bone disease and other isoforms.

Cholestasis due to biliary obstruction is typically associated with severe abdominal pain and



## Liver cell function and integrity

Pathophysiological chemistry	Biochemical mechanism	Pathology test(s)
Carbohydrate metabolism	Glycogenesis Glycogenolysis Glycolysis Gluconeogenesis	Glucose
Protein metabolism	Conversion of ammonia to urea; synthesis of albumin, some globulins, and clotting factors	Albumin* Total Protein* Globulins* Prothrombin Urea Ammonia
Lipid metabolism	Synthesis and catabolism of fatty acids, cholesterol, triglycerides and lipoproteins eg, VLDL	Cholesterol Triglycerides Bile acids
Organic anion metabolism	Conjugation Detoxification	Bilirubin* (conjugated and unconjugated)
Synthesis of some clotting factors, and storage of some vitamins and glycogen	Deficiency states	Prothrombin Glucose
Neoplastic transformation	Protein synthesis Oncofetal change	Alpha fetoprotein (AFP)
Hepatocyte injury	Inflammation Necrosis	ALT* AST*
Hepatobiliary injury	Increased enzyme synthesis, cell membrane injury and/or cholestasis	ALP* GGT*

\*denotes routine LFT panel.

Courtesy of Dr Matthew Meerkin.

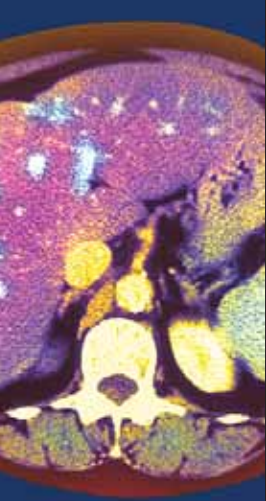
increased conjugated bilirubin. The normal bilirubin in this patient suggests either medication-induced cholestasis (see Table 2), or intrahepatic cholestasis or infiltration. Ultrasound is the best initial investigation in patients with persistently raised ALP of hepatic origin, to assess the biliary tree and liver parenchyma. Although elevated bile salts would confirm cholestasis, this test is not widely available, and is generally restricted to investigating suspected pregnancy-induced cholestasis and children with suspected abnormalities of bile metabolism. In this patient, ultrasound suggested multiple liver metastases. Other causes of intrahepatic cholestasis include rarer infiltrative conditions such as sarcoidosis or lymphoma, or autoimmune disease (primary biliary cirrhosis) and familial syndromes.

This patient also showed a markedly reduced

serum albumin. If liver disease is the sole cause of this finding, the liver damage must be both severe and long-standing. Other causes of low albumin include the acute phase response (a likely contributor in this man with malignancy), malnutrition, malabsorption, or protein loss through the kidney or bowel.

### Conclusions

These three cases illustrate some of the common patterns of liver enzyme abnormalities but are by no means exhaustive. It is important to remember that mild abnormalities of liver function only persist in about one-third of cases, so repeat testing is worthwhile to confirm an abnormality. Unless the patient appears unwell or unstable, or has a history of toxic exposure (for example, paracetamol), repeat testing could be done a few weeks later.



It is helpful to classify liver enzyme elevations as having a cholestatic or hepatocellular pattern. If cholestasis is suspected, imaging with ultrasound is the next logical investigation. In suspected hepatocellular injury, further laboratory testing

to exclude treatable causes of disease is indicated. Patterns of liver enzyme elevation can alter a clinician's assessment of disease probability, but are usually non-specific and need to be interpreted together with clinical findings.

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