Liver Disease

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Management of gastro-oesophageal varices

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Portal hypertension is usually a complication of liver disease and is associated with the development of a collateral circulation. This allows the diversion of portal blood into the systemic circulation through shunts which are commonly referred to as varices. Clinically significant shunts occur mostly around the gastro-oesophageal junction and give rise to gastro-oesophageal varices.

Development of varices

In patients with cirrhosis, the cumulative incidence of varices increases with time, rising from 12 to 90% over a 12-year follow-up period[1].

Prognosis of acute variceal bleeding

Most studies show a mortality of 20–50% after the first episode of variceal bleeding, with the mortality closely related to the severity of the underlying liver disease.

Table 1. Acute management of variceal bleeding (adapted from Ref 2).

Control of active variceal bleeding:

Resuscitation
- 2 large peripheral cannulae
- Cross match 6 units red cell concentrate
- Correct prothrombin time and platelet count
- Consider central venous access
- Consider airway intubation – if severe uncontrolled bleeding, severe encephalopathy or low oxygen saturation

Upper endoscopy
- As soon as patient is haemodynamically stable
- Variceal band ligation is the method of choice unless it is not available in which case sclerotherapy should be performed

Vasoconstrictors
- Terlipressin (Glypressin) or octreotide if no endoscopy

Failure to control active bleeding
- Insert Minnesota/Sengstaken tube until TIPSS or surgical treatment is arranged
- Specialist help should be considered at this stage

Prophylactic antibiotics either orally or systemically

TIPSS = transjugular intrahepatic portosystemic stent shunt/surgery.

Acute management of variceal bleeding

In common with the management of any gastrointestinal (GI) haemorrhage, the first step in the management of acute variceal bleeding is adequate resuscitation and airway protection to prevent aspiration. Coagulation abnormalities are normally corrected. Early endoscopy (as soon as the patient is haemodynamically stable) is recommended because it not only enables accurate diagnosis but also allows the deployment of effective therapeutic intervention, namely, variceal band ligation or sclerosant injection (Table 1).

We recommend the algorithm published in the British Society of Gastroenterology guidelines for the management of variceal haemorrhage (reproduced in Fig 1)[3].

There are four modalities of treatment:
1 Pharmacological therapy.
2 Endoscopic therapy.
3 Balloon tamponade.
4 Transjugular intrahepatic porto-systemic stent shunt (TIPSS)/surgery.

Pharmacological therapy

Two classes of drugs are used for pharmacological treatment:
- vasopressin or its analogues, and
- somatostatin or its analogues.

Vasopressin and terlipressin (Glypressin®) are the only licensed drugs for this indication in Europe, although the former is no longer recommended. These drugs have systemic vasoconstricting and portal hypotensive effects. The only other drug in common use in the UK is octreotide, a somatostatin analogue which causes selective splanchnic vasoconstriction and reduces portal pressure. These drugs should be used if more definitive therapy is delayed or unavailable. One school of thought considers that administration of these drugs before endoscopic therapy may improve results.

Endoscopic therapy

Injection sclerotherapy and band ligation can both control acute bleeding. Variceal

band ligation is our current method of choice because it is associated with fewer side effects than sclerotherapy (particularly ulceration) and is at least as effective[2]. Some people prefer to use sclerotherapy to control acute bleeding when it is severe and subsequently band ligation to eradicate varices. Injection of tissue adhesives or thrombin may be used in the treatment of gastric varices, but good evidence is lacking in this field.

Balloon tamponade

This treatment is highly effective and arrests bleeding in up to 90% of cases, although rebleeding occurs in 50% when the balloon is deflated[4]. The Minnesota or Sengstaken-Blakemore tube should be inserted only by experienced staff. It should be passed via the mouth well into the stomach prior to inflation of the gastric balloon with 300 ml air. Care must be taken during inflation; if there is any pain, inflation must be discontinued and the balloon withdrawn. Traction should be applied to maintain the position of the balloon at the gastro-oesophageal junction. The oesophageal balloon should be inflated only if bleeding continues, deflated for 30 min every 4–6 hours to prevent oesophageal wall necrosis, and tamponade continued for up to 12 hours.

Although this form of treatment is potentially life-saving, it is only a *temporary* measure and should be followed by definitive endoscopic treatment.

Transjugular intrahepatic portosystemic stent shunt/surgery

TIPSS is a radiological procedure which has become increasingly available to most centres over the last 10 years. The procedure creates a communication between the portal and systemic circulations through the liver parenchyma (Fig 2). This tract is maintained open by the insertion of an expandable 8–12 mm

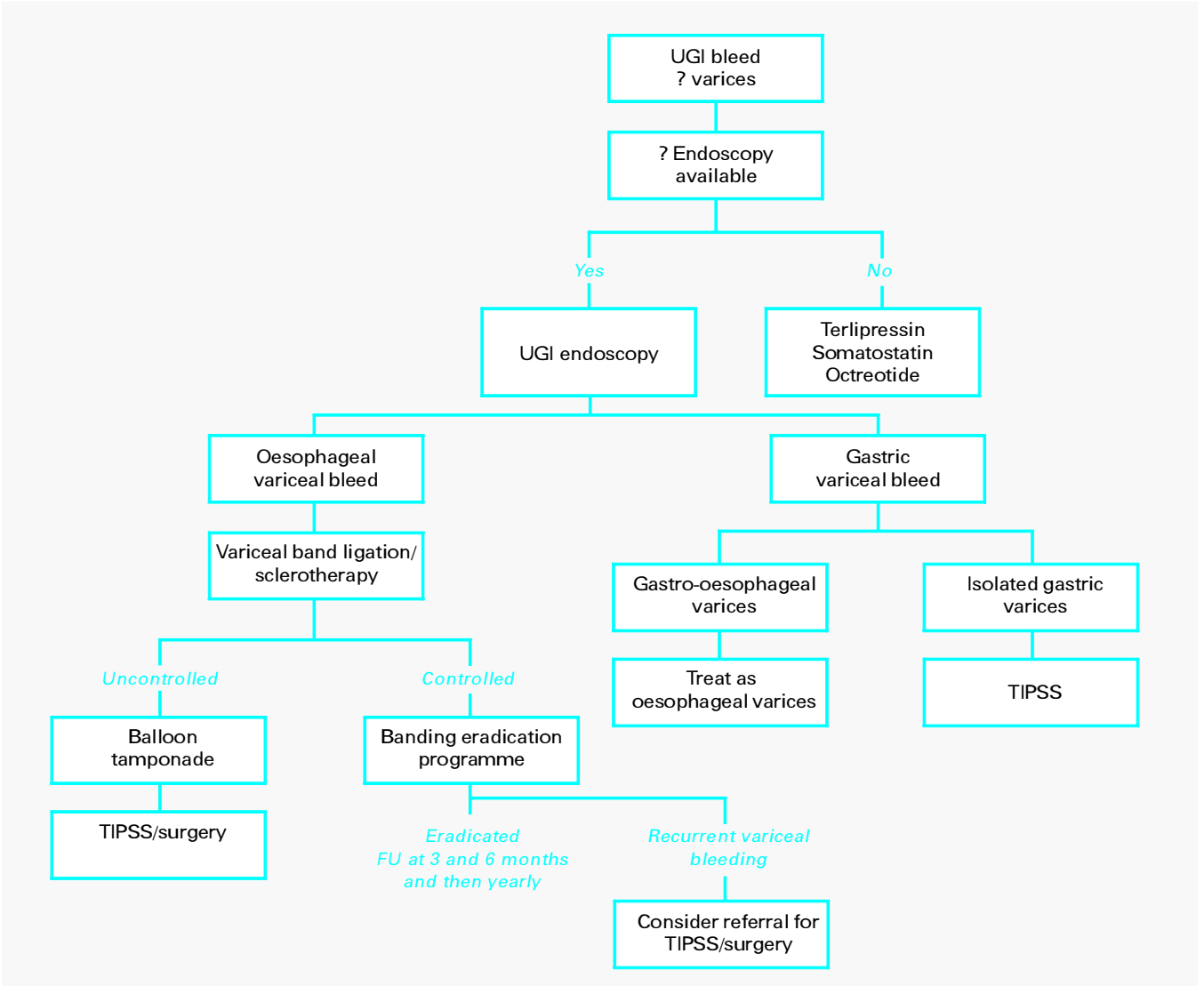

Fig 1. Algorithm for the management of variceal haemorrhage (FU = follow-up; TIPSS = transjugular intrahepatic portosystemic stent shunt; UGI = upper gastrointestinal)[3].

metal stent. It is widely accepted that TIPSS can be performed successfully in cases of uncontrolled variceal bleeding and is associated with rapid cessation of bleeding. Insertion of TIPSS may be complicated by encephalopathy (20% of patients) and the gradual development of shunt insufficiency[5] in most patients over time, necessitating regular Doppler or portographic surveillance with angiographic intervention to dilate stenosed shunts when detected.

TIPSS has a lower morbidity and mortality than surgical shunt procedures or oesophageal transection and has become the treatment of choice as rescue therapy for patients who fail endoscopic therapy. The mortality rate of shunt surgery or oesophageal transection is high in patients with severe liver disease, so these procedures should be reserved for those patients in whom technical problems prevent TIPSS.

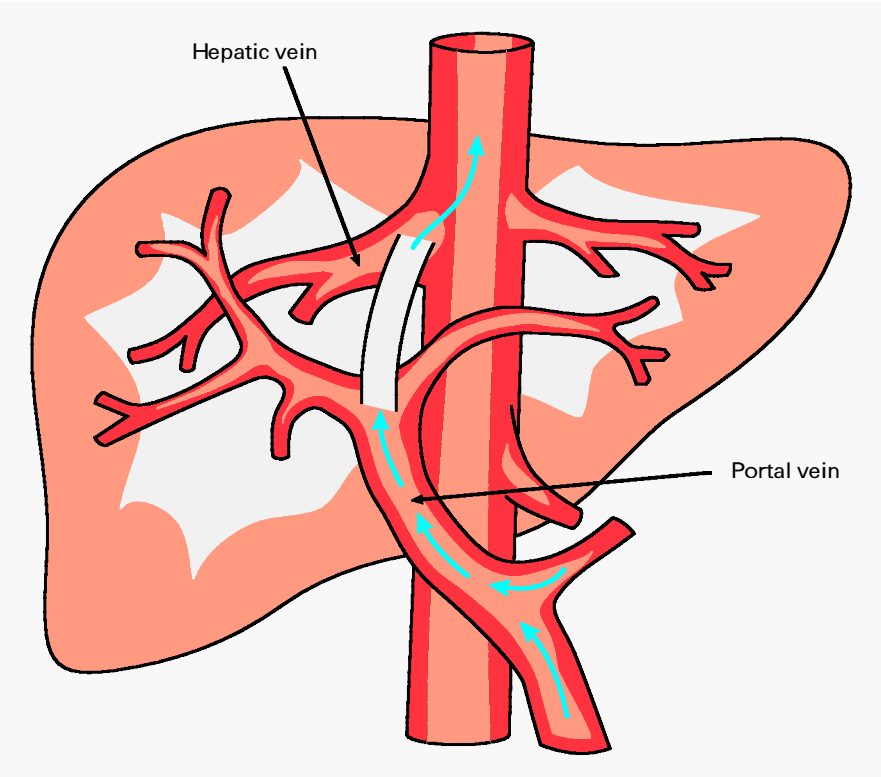

Fig 2. Schematic representation of a transjugular intrahepatic portosystemic stent shunt (TIPSS) (a radiologically placed stent through the liver parenchyma) decompressing the portal circulation into the systemic circulation.

Bleeding from gastric or ectopic varices and portal hypertensive gastropathy

Gastric varices are the source of bleeding in 10–36% of patients with variceal haemorrhage[6]. Endoscopic therapy with variceal band ligation is generally unhelpful. Attention has therefore focused on control of bleeding with thrombin or tissue adhesives. However, further randomised studies are needed before these methods become widely accepted. In the meantime, bleeding may be controlled with pharmacological therapy before proceeding to TIPSS.

Bleeding from portal hypertensive gastropathy accounts for 5–8% of bleeding episodes in cirrhosis[6]. However, major bleeding is uncommon and its management usually consists of adequate fluid resuscitation and blood transfusion, pharmacological therapy, TIPSS or surgery, depending on the severity of bleeding and the degree of liver impairment. Endoscopic therapy in the form of argon plasma coagulation may be useful.

Antibiotics in variceal bleeding

Bacterial infections are common in patients with cirrhosis. The overall incidence of bacterial infections in cirrhotic patients admitted with GI

GLOSSARY FOR CME LIVER DISEASE

AFP	alpha-fetoprotein
AIH	autoimmune hepatitis
ALP	alkaline phosphatase
ALT	alanine aminotransferase
anti-HBc	antibody to hepatitis B core antigen
anti-HBe	antibody to hepatitis B e antigen
AST	aspartate aminotransferase
BP	blood pressure
CHC	chronic hepatitis C
CT	computed tomography
EDTA	ethylene diamine tetraacetic acid
ELISA	enzyme-linked immunosorbent assay
FBC	full blood count
FE	iron
GGT	gamma-glutamyl transferase
GI	gastrointestinal
GP	general practitioner
HAV	hepatitis A virus
Hb	haemoglobin
HBeAg	hepatitis B e antigen
HBIg	hepatitis B immunoglobulin
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
IFN	interferon
INR	international normalised ratio
LFT	liver function test
LKM	liver-kidney microsomal antibody
MRI	magnetic resonance imaging
PBC	primary biliary cirrhosis
PCR	polymerase chain reaction
PEG	polyethylene glycol
PFT	pulmonary function test
PMN	polymorphonuclear neutrophil
prn	as required
PSC	primary sclerosing cholangitis
SAAG	serum-ascites albumin gradient
SSRI	selective serotonin reuptake inhibitor
TFT	thyroid function test
TIBC	total iron binding capacity
TIPSS	Transjugular intrahepatic portosystemic stent shunt/surgery
ULN	upper limit of normal
WBC	whole blood cell count

haemorrhage is 44% (pooled data from eight published prospective studies). Spontaneous bacterial peritonitis is the commonest manifestation of infection which is usually caused by enteric Gram-negative bacteria (mainly *Escherichia coli*), although Gram-positive organisms are also found in cases where the predominant site of infection is the lower respiratory tract. Mortality has been shown to be higher in these patients than in non-infected patients[7,8]. It has also been shown that infections also predispose to recurrent variceal haemorrhage[9]. A meta-analysis of five trials of short-term antibiotic prophylaxis in variceal bleeding showed both a decrease in the number of infections in treated patients and also improved survival[10]. The current recommendation is oral administration of either norfloxacin (400 mg twice daily) or ciprofloxacin (500 mg twice daily) for seven days in all patients with cirrhosis admitted with GI haemorrhage.

Prevention of rebleeding (secondary prophylaxis against variceal haemorrhage)

The majority of patients will rebleed within six months of endoscopic control of their initial bleeding episode, more commonly within the first few weeks. Further measures are therefore necessary to reduce the risk of rebleeding. These are:

- further endoscopic therapy
- pharmacological treatment or
- portosystemic shunt creation either by surgery or TIPSS.

Endoscopic therapy

A meta-analysis of eight trials comparing sclerotherapy with no treatment in the prevention of variceal rebleeding showed reductions in rebleeding and mortality in the sclerotherapy group[11]. The advantages of variceal band ligation over sclerotherapy have been described above; it is now generally accepted that band ligation performed at 1–2 weekly intervals until varices are eradicated is the method of choice for the prevention of variceal rebleeding in most units[6].

Pharmacological therapy

Beta-blockers are the most widely used drugs to prevent rebleeding. Propranolol, and to a lesser extent nadolol, have been studied extensively in a number of randomised trials against placebo. Two meta-analyses have confirmed their efficacy in decreasing the likelihood of rebleeding and lowering mortality[11,12]. Most studies have found sclerotherapy and beta-blockers have similar efficacy in preventing rebleeding, although sclerotherapy is associated with more complications.

A meta-analysis of trials comparing sclerotherapy with sclerotherapy and beta-blockers showed no advantage for combination therapy[11]. Studies are needed comparing the efficacy and tolerance of band ligation and pharmacological therapy in secondary prophylaxis against variceal bleeding.

Transjugular intrahepatic portosystemic stent shunt/surgery

TIPSS is an accepted rescue treatment for patients with variceal haemorrhage refractory to endoscopic treatment. A meta-analysis of trials comparing TIPSS with endoscopic therapy showed that TIPSS was much more effective in reducing rebleeding, although associated with an increased risk of encephalopathy. Survival was the same with both treatments[13] and the cost was similar.

There is clearly a trade-off between reduction in rebleeding with TIPSS and an increase in encephalopathy. The decision regarding the selection of which approach is best for secondary prophylaxis will depend on the individual patient, local expertise and service availability.

Surgery

A meta-analysis of trials comparing shunt surgery with sclerotherapy to prevent variceal rebleeding showed reduced bleeding rates but higher encephalopathy rates in the surgical group although there was no difference in mortality[11].

Liver transplantation

Patients with advanced liver disease and a variceal haemorrhage should be considered for transplantation.

Primary prophylaxis against variceal bleeding

The poor prognosis following a variceal bleed has led to the development of strategies to prevent rebleeding (Fig 3). The two modalities of treatment most extensively investigated are pharmacological agents (mainly beta-blockers and nitrates) and endoscopic treatments.

All patients with cirrhosis should have a screening endoscopy to confirm the

Key Points

Acute variceal bleeding has a mortality of 20–50%

Treatment of acute variceal bleeding consists of resuscitation, correction of coagulation abnormalities and early endoscopic therapy or balloon tamponade/vasoconstrictor therapy

Antibiotic prophylaxis improves survival in acute variceal bleeding

Prevention of rebleeding is achieved by variceal band ligation, beta-blocker therapy or transjugular intrahepatic portosystemic shunt/surgery

Patients with cirrhosis should have a screening endoscopy and those found to have medium/large oesophageal varices should be offered treatment with either beta-blockers or variceal band ligation

KEY WORDS: CPD, cirrhosis, gastro-oesophageal varices, primary prophylaxis, secondary prophylaxis, tamponade, transjugular intrahepatic portosystemic stent shunt/surgery, variceal band ligation

presence of varices. Primary prophylactic therapy should then be offered to those with medium or large varices (which are at high risk of bleeding). If the patient has small varices, surveillance endoscopies should be performed annually. If no varices are found, endoscopy should be repeated every two years.

Pharmacological agents

Propranolol is the mainstay of treatment. It achieves a reduction in portal pressure gradient by causing splanchnic vasoconstriction and reducing cardiac output. A meta-analysis[14] has shown both a significant reduction in the risk of bleeding (by about 40%) for propranolol compared with placebo and a trend towards improved survival.

The combination of nadolol and isosorbide mononitrate was compared with nadolol monotherapy by Merkel and colleagues[15,16]. The combination treatment reduced bleeding rates although mortality was unchanged. Worth noting, however, is the high incidence of side effects in the combination therapy group which necessitated withdrawal of 11% of patients compared with only 4% in the nadolol alone group[15,16].

Endoscopic therapy

A large number of trials have compared sclerotherapy with no treatment for the prevention of bleeding in cirrhosis. The results are variable and no firm conclusion can be drawn because of the marked heterogeneity between these studies. In view of the recognised complications of sclerotherapy, it cannot be recommended for primary prophylaxis against variceal bleeding.

A recent meta-analysis of trials comparing band ligation with no therapy showed a clear reduction in bleeding and improvement in survival. When ligation was compared with beta-blockers, patients treated endoscopically had a lower incidence of first haemorrhage but no difference in mortality[17].

The two treatments seem broadly similar, with band ligation perhaps better at reducing bleeding. The choice of therapy will depend on the local centre's expertise and on the individual patient. Those likely to be poorly compliant with drug therapy may well be better treated by band ligation.

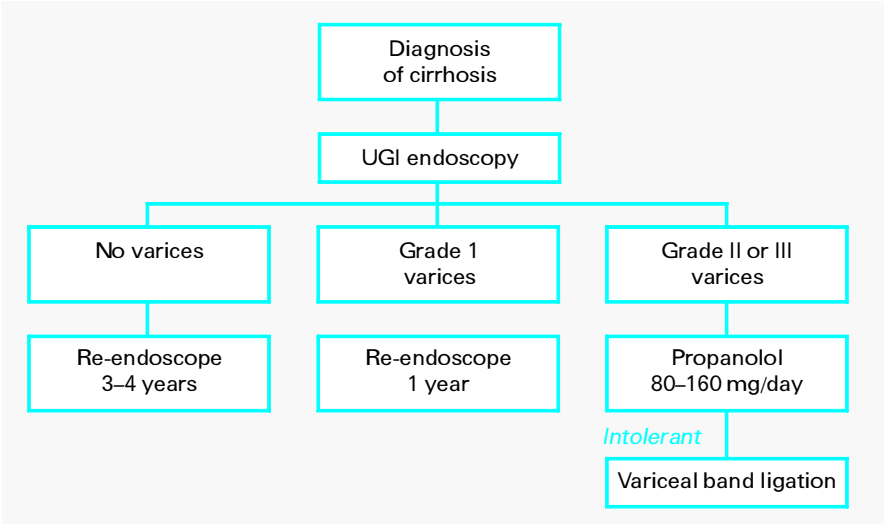

Fig 3. Algorithm for variceal surveillance and primary prophylaxis against variceal bleeding (UGI = upper gastrointestinal)[3].

Conclusion

Variceal haemorrhage is a medical emergency with a high mortality. Survival is closely related to the severity of liver disease and is little influenced by most of the range of treatments available. Liver transplantation is the only therapy likely to have a major impact on these patients with severe liver disease, particularly if complicated by variceal bleeding.

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Assessment and management of chronic hepatitis C infection

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Hepatitis C infection

It is estimated that 0.5–1% of the UK population is infected with hepatitis C virus (HCV) and 170 million people worldwide. The commonest route of infection in the UK is injecting drug use, although there are still a significant number of people whose infection was contracted from infected blood products prior to the introduction of HCV screening in 1991. The virus is parenterally transmitted, so other risk factors include:

- vertical transmission during childbirth
- transmission during medical procedures
- tattooing
- body piercing, and
- sexual transmission[1].

Key Points

- **Hepatitis C is parenterally transmitted**
- **Hepatitis C virus (HCV) leads to chronic infection in 85% of those exposed**
- **Chronic hepatitis C causes progressive liver damage**
- **Liver damage is silent in the majority**
- **Liver biopsy is the most accurate way to assess severity of liver damage**
- **Antiviral treatment is recommended in most patients with progressive liver disease**
- **Antiviral treatment achieves viral clearance in 30-56% (depending on regimen)**
- **HCV genotypes 1 and 4 are more resistant to antiviral therapy than genotypes 2 and 3**

KEY WORDS: chronic hepatitis, hepatitis C virus, interferon, PEGylated interferon, ribavirin, viral hepatitis

Acute hepatitis C infection

In the vast majority of cases acute HCV infection is asymptomatic, leading to flu-like symptoms in some subjects and clinical jaundice in less than 20%. Acute hepatitis C is rarely diagnosed, but if encountered should be treated promptly, as recent evidence has shown sustained viral clearance rates in excess of 90%[2].

Chronic hepatitis C infection

Chronic infection is established in about 85% of those exposed and is often silent, which probably leads to underestimation of its prevalence. Common routes to diagnosis are:

- routine screening by the blood transfusion service
- direct request for testing from the patient
- incidental discovery of abnormal liver function tests during investigation of unrelated symptoms.

Chronic hepatitis C (CHC) infection is characterised by an immune-mediated hepatitis associated with progressive fibrosis. It is the severity and rate of progression of this fibrosis that dictates the mortality and morbidity associated with CHC. About one-third of patients have an indolent course to their disease lasting at least 30 years before significant fibrosis develops, but most of them will progress to significant liver fibrosis or cirrhosis within 20 years of infection[3].