Signs and symptoms of chronic viral hepatitis

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**Introduction**

Acute infection with hepatitis B virus (HBV) or hepatitis C virus (HCV) can result in chronic hepatitis if the infection persists for more than six months. The rate of spontaneous clearance varies according to the virus, the age at onset of infection and other factors.

Spontaneous clearance of HCV generally occurs during the first six months of infection in approximately a quarter of people with the infection, with the remainder developing chronic hepatitis. Although gradual histological progression occurs in most people, the condition is often asymptomatic for an extended period of time. Symptoms arise with the development of complications of advanced liver disease, but non-specific symptoms and impaired quality of life are common among those with earlier stages of liver disease. Cirrhosis occurs in an estimated 15–20% of people who develop chronic HCV infection, 15–40 years after the original infection. Among those who develop cirrhosis, liver failure occurs in 20–30% and hepatocellular carcinoma (HCC) develops in 10–15% over 10 years. Estimates of disease progression in hepatitis C are outlined in Figure 7.1.

The natural history of HBV infection is primarily determined by the age of the person at the onset of infection. When acquired at birth or during early childhood, the risk of developing chronic infection is high, with only 2% of infants spontaneously clearing the virus within three years of infection and 15% clearing the virus within 20 years. Among people with perinatally-acquired HBV, 40–50% of males and 15% of females die from the liver-related causes.

In the case of adult-acquired HBV infection, however, the situation is reversed, with spontaneous clearance being the rule. Acute liver failure occurs rarely, and only 3–5% of adults with acute infection go on to develop chronic HBV infection. In many cases, chronic HBV infection does not result in symptoms or long-term problems, although 20–30% of people will progress to cirrhosis.

**Key points**

- The presence of significant liver disease in patients may not be apparent from symptoms or clinical examination. Conversely, multiple symptoms in chronic hepatitis infection do not necessarily mean the existence of significant liver disease.
- Progressive liver disease in chronic hepatitis B often involves hepatic ‘flares’, whereas progressive disease is often asymptomatic in chronic hepatitis C.
- There is a poor correlation between biochemical and virological markers of chronic viral hepatitis and symptoms and signs, particularly in chronic hepatitis C.

These differences in outcome between perinatal and adult-acquired infection are outlined in Figure 7.2. Of those with compensated cirrhosis, 20–30% will develop liver failure (decompensated cirrhosis) and 10–20% will develop HCC over the next ten years. Survival rates are high among those with compensated cirrhosis but much lower among those with liver failure (85% versus 25% at five years).

**Symptoms and signs of chronic viral hepatitis**

Chronic viral hepatitis is frequently hidden due to the asymptomatic nature of liver disease in a large proportion of people and the slowness or absence of progression to advanced liver disease. The absence of symptoms and abnormal clinical signs, therefore, does not exclude significant liver disease. However, early diagnosis and treatment may improve prognosis and, where appropriate, patients should be offered treatment options.

Although there is a great deal of overlap, symptoms and signs of chronic viral hepatitis can be divided into those associated with:

- Early or slowly progressive liver disease
- Progressive liver disease
- Advanced liver disease complications
- Extrahepatic manifestations

In this classification, ‘early or slowly progressive liver disease’ includes people with chronic hepatitis C who progress slowly and may have early fibrosis.
'Progressive liver disease' covers people who progress to cirrhosis or, in the case of chronic HBV infection, have clinical evidence of progressive disease such as hepatitis 'flares' but retain adequate liver function (e.g. compensated cirrhosis).

'Advanced liver disease complications' includes people who have developed clinical liver failure (decompensated cirrhosis, e.g. hepatic encephalopathy and failure of synthetic function with increases in International Normalised Ratio [INR]), portal hypertension (e.g. ascites, oesophageal varices) and hepatocellular carcinoma (HCC). 'Extrahepatic manifestations' refers to a broad range of clinical conditions associated with either chronic hepatitis B or chronic hepatitis C.

Clearly these groups are not mutually exclusive. For example, it is possible to have progressive liver disease and extrahepatic manifestations of chronic hepatitis. In addition, there may be little clinical distinction between 'early or slowly progressive disease' and 'progressive disease'. A long asymptomatic phase followed by signs associated with cirrhosis or decompensation is not uncommon.

**Early or slowly progressive liver disease**
Symptoms of chronic viral hepatitis associated with early and/or slowly progressive liver disease are generally non-specific. Individuals frequently complain of tiredness, anorexia, nausea, intolerance to fatty foods, and abdominal discomfort, particularly in the right upper quadrant region. Others report general feelings of being unwell but are unable to elaborate further. Fevers and night sweats can also occur.

A number of recent studies have shown that people with chronic HCV infection score poorly on many quality-of-life parameters, including a range of physical and psychological measures of wellbeing. Again, these impairments are relatively non-specific, and include reductions in general health perception, mental health, physical function, social function and vitality. These measures may also be impaired in many people with chronic hepatitis B. Successful clearance of HCV through antiviral therapy has been shown to improve quality-of-life scores.

The major feature of the symptomatology of early or slowly progressive liver disease in chronic viral hepatitis is its highly variable nature. For many people, this stage of liver disease, which may be the only stage they experience, is completely asymptomatic. On the other hand, many people have considerable symptoms despite the presence of mild liver disease or the absence of biochemical evidence of liver inflammation (normal alanine aminotransferase [ALT] and aspartate aminotransferase [AST] levels). In fact, in chronic hepatitis C there is little correlation between the ALT level and presence of symptoms. Furthermore, the stage of liver disease (prior to liver failure) and the viral load in chronic hepatitis C have a poor association with the extent of symptoms.
People with early or slowly progressive liver disease generally have few clinical signs associated with their chronic viral hepatitis. The most common clinical examination reveals either no abnormal findings or mild hepatomegaly. Presence of peripheral stigmata of chronic liver disease, such as multiple spider naevi and palmar erythema, would generally indicate cirrhosis.

**Progressive liver disease**

Although the vast majority of people with chronic viral hepatitis will not develop advanced liver disease complications, many will eventually have progressive liver disease. The symptoms covered above may also be present in progressive liver disease.

In chronic hepatitis B, particularly in the case of perinatal or early childhood infection, a prolonged asymptomatic period (immune tolerance phase) is followed by a more symptomatic period (reactivation-clearance phase) in which flares of clinical hepatitis may occur as the body's immune system attempts to clear infection. These flares are generally milder than an acute hepatitis B clinical presentation, however, they often consist of similar symptoms and signs. These include lethargy, nausea, anorexia, food intolerance, abdominal discomfort and jaundice. These clinical flares in chronic hepatitis B are closely associated with biochemical evidence of increased hepatic inflammation. Marked elevations of ALT and AST together with increased serum bilirubin levels are often seen. A small proportion of people each year in this reactivation/clearance phase will 'seroconvert', initially from hepatitis B 'e' antigen positive (HBeAg+) to HBeAg-negative (generally with development of anti-HBe). In some cases there is subsequent loss of hepatitis B surface antigen (HBsAg). People with frequent flares who have not seroconverted may experience faster disease progression and are at high risk of cirrhosis and HCC. In addition, people who have entered the clearance phase and seroconverted to anti-HBe can have reactivation of disease at a later date with the emergence of 'pre-core mutant' disease. This stage of hepatitis B is characterised by negative HBeAg but abnormal liver function tests (LFTs) and elevated HBV DNA. This form of chronic hepatitis B is also associated with more aggressive disease. All patients with chronic hepatitis B (HBsAg positive), particularly with abnormal LFTs or elevated HBV DNA (> 103 IU/mL) should be referred for specialist review and consideration of therapeutic intervention.

In chronic hepatitis C, clinical hepatitis flares are rare and people often progress to cirrhosis without development of significant symptoms. Prior to development of liver failure, there may be little to distinguish a person with early or slowly progressive liver disease from a person with progressive liver disease. If present, symptoms are generally non-specific, as with early and slowly progressive liver disease. Factors associated with progressive liver disease in chronic hepatitis C are listed in Table 7.1. Peripheral stigmata of chronic liver disease, such as spider naevi, liver nails and palmar erythema, may develop if there is progression to cirrhosis. However, a completely normal clinical examination may also be found in the presence of cirrhosis related to both chronic hepatitis B and hepatitis C.

**Advanced liver disease complications**

Advanced liver disease complications of both chronic HBV and HCV infection consist of liver failure (decompensated cirrhosis), often in association with signs of portal hypertension such as refractory ascites and variceal bleeding, and HCC. In chronic hepatitis C, HCC only develops if there is underlying severe fibrosis or cirrhosis. In contrast, as HBV itself is oncogenic, HCC can develop in people with chronic hepatitis B without significant liver fibrosis.
Symptoms and signs of liver failure are the same for chronic HBV and HCV, and are similar to symptoms and signs associated with other causes of decompensated cirrhosis. Consistent with the underlying lack of synthetic function (hypoalbuminaemia and coagulopathy), early symptoms of liver failure may include ankle and mild abdominal swelling, and easy bruising. Increasing lethargy is generally also a feature. Clinical examination should reveal some peripheral stigmata of chronic liver disease, as well as some evidence of either peripheral oedema or ascites. Later signs may include jaundice, which indicates a poor prognosis in the presence of liver failure, loss of hair and gynaecomastia. Clinical evidence of portal hypertension may include abdominal venous distension, splenomegaly and ascites. Patients who have ascites may develop spontaneous bacterial peritonitis (SBP). Patients with unexplained fever or encephalopathy should raise the suspicion of SBP and they should be referred for diagnostic paracentesis. In addition, the presence of peripheral neuropathy and cerebellar ataxia may suggest alcohol as a contributing cause of liver disease.  

A history of haematemesis in a person with other evidence of advanced liver disease suggests the presence of oesophageal varices related to underlying portal hypertension. Hepatic encephalopathy also may be present in advanced liver disease and may be subclinical in early stages. A history of reversal of diurnal sleep patterns, forgetfulness or inappropriate behaviour may signal the onset of early hepatic encephalopathy. Presence of either hepatic encephalopathy or oesophageal varices indicates a poor prognosis.

Table 7.2 summarises the different signs and symptoms related to stages of liver disease in chronic hepatitis B and C.

### Extrahepatic manifestations
Extrahepatic manifestations, although uncommon, represent clinically important aspects of hepatitis B and C (Table 7.3). Specific treatment can be directed towards these conditions.

Dermatological presentations include porphyria cutanea tarda (PCT), lichen planus and vasculitic rashes associated with cryoglobulinaemia. These presentations should alert the clinician to the possibility of chronic viral hepatitis. In patients with PCT, which is typically associated with chronic hepatitis C, blistered lesions, which are exacerbated by exposure to the sun, occur on the dorsum of the hands and forearms, and ferritin levels are often mildly elevated. These patients respond very well to venesection.

Rheumatological manifestations include arthropathy, Sjogren’s syndrome and polyarteritis nodosa. A high serum globulin level, often associated with positive antinuclear antibody (ANA) and rheumatoid factor, may indicate the presence of cryoglobulinemia, which may be associated with systemic complications such as glomerulonephritis and vasculitis.

Other haematological abnormalities include thrombocytopenia and leucopenia. Thrombocytopenia may be the result of hypersplenism or drug therapy, or it may be immune-mediated. Neurological complications may be related to cryoglobulinemia and present with mononeuritis of cranial or peripheral nerves. Thyroid disease may be subclinical. A variety of thyroid diseases have been described in association with chronic viral hepatitis. Patients who test positive for ANA are more prone to developing thyroid disorders, particularly when treated with interferon. These thyroid disorders, however, are generally reversible.

### Assessment of the presence and stage of disease
An assessment of the presence and stage of disease often requires a step-wise investigation of serological, virological, biochemical, ultrasonographic and histological markers of viral hepatitis and liver disease. In addition, clinical examination may provide some indication of the stage of disease, particularly when advanced liver disease is present. The results of these investigations may determine access to antiviral treatment, which is funded under Section 100 of the Pharmaceutical Benefits Scheme (Chapter 11).

### Serological markers
In hepatitis C, a positive HCV antibody result indicates prior or current infection but does not distinguish between these two conditions.

In hepatitis B, serological testing provides useful information on the presence of active infection. HBsAg is a marker of current infection. It may disappear

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**Table 7.1: Factors associated with progression to advanced liver disease in chronic hepatitis C**

- Age at acquisition of infection (>40 years)
- Heavy alcohol intake (>40 grams/day)
- Male gender
- Longer duration of infection
- Moderate to severe hepatic fibrosis on baseline liver biopsy
- Coinfection with HIV and/or chronic hepatitis B
- Obesity

Note: There is no evidence for an association between HCV viral load and risk of disease progression.

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following acute infection or persist in a person who has HBV infection. Anti-HBs appears following the disappearance of HBsAg, and is a marker of both naturally acquired and vaccine-induced immunity. The presence of anti-hepatitis B core (HBc) IgM generally indicates recent infection since it usually appears following acute infection and disappears within a year. Occasionally, anti-HBc IgM may be positive during hepatic flares in people with chronic hepatitis B. Anti-HBc IgG can persist indefinitely following an infection, and signifies exposure to HBV.

Most people exposed to HBV as adolescents or adults clear the infection and will test anti-HBc positive (anti-HBc+) and HBsAg negative. HBeAg is a marker of viral replication and hence infectivity. Anti-HBe generally develops as HBeAg disappears, signalling resolution of acute infection or cessation of replication. More complete clearance of HBV infection is indicated by development of anti-HBs. Refer to Table 7.2 for a summary of serological and virological markers of acute and chronic hepatitis.

**Virological tests**

HCV RNA testing by polymerase chain reaction (PCR) can indicate the presence of HCV, as well as viral load. A qualitative HCV RNA test generally distinguishes between a person who has chronic hepatitis C and a person who has cleared HCV either spontaneously or during treatment. People who have cleared HCV will continue to test positive for the anti-HCV but will be negative for HCV RNA. Thus, if symptoms and signs of active infection are present in a person with normal serum ALT levels who is HCV antibody positive and HCV RNA negative, a cause other than hepatitis C should be sought.

On the other hand, the vast majority of people with elevated serum ALT levels who test positive for HCV antibody, particularly in the presence of a risk factor...
for infection, have active infection (viraemia). In these people, HCV RNA will be positive and of no use in assessing the severity of the disease. A quantitative HCV RNA or viral load test does not provide information on the stage of disease because there is little or no correlation between the HCV viral load and the extent of hepatic fibrosis or risk of disease progression (in distinct contrast to the situation with HIV). However, HCV viral load has prognostic value with regard to response to antiviral therapy, and the HCV genotype is even more predictive of response. HCV viral genotyping is essential in determining the likely response and optimal duration of antiviral treatment (Chapter 11).

HBV DNA is also a marker of active replication and can be assessed quantitatively to predict likely response to antiviral treatment, with low levels being associated with better outcome. The vast majority of people who are HBeAg+ will be positive on HBV DNA testing.

Liver function profile
The serum ALT level may give an indication of hepatic inflammation although levels may be normal despite progressive liver disease. Nevertheless, people with either chronic HBV or HCV who have consistently normal ALT levels are at low risk of progression to cirrhosis. Although people with abnormal ALT levels are at increased risk of progressive liver disease, the level of ALT in chronic hepatitis C is a relatively poor predictor of disease stage or disease progression. In contrast, in chronic hepatitis B recurrently high ALT levels generally indicate more active underlying disease and risk of disease progression. An 'inverted' AST/ALT ratio (higher AST than ALT) may indicate underlying cirrhosis in either chronic HBV or HCV infection. Albumin level (along with the prothrombin time) gives an indication of the synthetic function of the liver. Hypoalbuminaemia and prolonged prothrombin time indicate decompensated cirrhosis. Evidence from a cohort of people with chronic hepatitis C demonstrated that one of the strongest prognostic measures was albumin level, with higher rates of progression to liver disease complications among people with levels below 35 g/L, particularly if less than 30 g/L.

Liver imaging
Abdominal ultrasound is used to assess the liver and biliary tree, as other causes of right upper quadrant pain, such as gallstones, often need to be excluded. In addition, abdominal ultrasound helps to screen for HCC and to assess for small amounts of ascites where doubt exists. However, a normal ultrasound does not exclude cirrhosis and this investigation is probably unnecessary in a person with no clinical evidence of chronic liver disease. Alpha-fetoprotein (AFP) level should also be measured at baseline, and monitored every six months, especially in people with chronic hepatitis B and those with cirrhosis, since this is a useful marker of HCC.

Other investigations
Other tests are used to identify complications or co-existing problems that may impact on prognosis and treatment decisions. For example, a low platelet count may signal the development of portal hypertension and hypersplenism. The presence of co-existing HBV, HCV or HIV may alter prognosis and treatment options. In treating hepatitis C, hepatitis A virus (HAV) and HBV status should be determined in order to offer vaccinations against superinfection by these organisms, which might worsen prognosis. Similarly, in treating hepatitis B, vaccination against HAV should be considered.

Thyroid function tests are useful to exclude associated thyroid disorders. They also should be conducted prior to antiviral therapy, which has been known to cause toxicity to the thyroid gland. Ferritin levels, alpha-1-antitrypsin, caeruloplasmin and copper levels are measured to exclude the other hepatic pathologies: haemochromatosis, alpha-1-antitrypsin deficiency and Wilson’s disease. ANA, anti-smooth muscle (SMA) antibody (SMA) and liver kidney microsomal antibody (LKM) are markers for auto-immune liver disease. Low titres of ANA and SMA may be present in liver disease and may not indicate auto-immune liver disease.
Liver biopsy
Liver biopsy for HCV was previously performed in the majority of patients undergoing assessment for antiviral therapy and was required under Section 100 guidelines. However, the requirement for liver biopsy has now been dropped and it is anticipated that the number of HCV patients undergoing treatment will increase. Liver biopsy is now not necessary in many patients prior to treatment with pegylated interferon and ribavirin. Biopsy remains, however, the definitive test for staging of liver disease and can still be an important tool in determining prognosis and guiding therapeutic decisions in selected patients.

In patients with chronic hepatitis B, liver biopsy remains a valuable investigation as fibrosis progression is far less predictable. Patients are frequently frightened of the invasive nature of this test. In addition, some patients mistakenly believe that they will not receive pain relief if they disclose a history of drug use. This should be addressed by explaining that liver biopsy is the most accurate way to assess the level of liver damage and by offering information about the procedure itself and the expertise of the people performing the biopsy. The role of other non-invasive methods of assessing liver fibrosis remains to be established.

Patients are often puzzled because of the lack of correlation between their symptoms, their blood tests and the serious consequences that can be associated with viral hepatitis. It is important to stress that the absence of symptoms, signs and abnormal ALT levels does not exclude significant liver damage.

A summary of the investigations used in chronic viral hepatitis is provided in Table 7.4.

Clinical examination
Physical examination of patients with suspected or confirmed viral hepatitis consists of general inspection as well as attention to specific signs of chronic liver disease and associated systemic disorders. Examination should include:

- General appearance and mental state of the patient
- Peripheral examination of the hands (for palmar erythema, Dupuytren’s contracture, leuconychia, blistered lesions)
- Examination of the arms or trunk (for abnormal bruising, spider naevi, loss of hair and gynaecomastia)
- Inspection for jaundice, anaemia and parotid enlargement
- Inspection of the abdomen (for evidence of collateral circulation, herniae, hepatomegaly, splenomegaly and ascites)
- Signs of fever or encephalopathy
- Peripheral neuropathy and cerebellar ataxia (which suggest alcohol as a cause of liver disease)
- A history of reversal of diurnal sleep patterns, forgetfulness or inappropriate behaviour, which may signal the onset of early hepatic encephalopathy.

Summary
Chronic hepatitis C and chronic hepatitis B are generally asymptomatic and therefore frequently hidden to both the patient and the clinician. Since a history of risk behaviour is often not disclosed to doctors, a reason to offer testing and diagnosis may not present itself. When symptoms do occur, they are largely non-specific and common symptoms that may be the result of a myriad of diseases. Consequently, the diagnosis of HCV or HBV infection can be easily missed. Being alert to the possibility of chronic viral hepatitis as a cause of many clinical presentations will allow early diagnosis and the offer of treatment.

Blood tests and ultrasound imaging help to assess hepatic function and the presence of complications and other associated disease that may be critical to decisions about prognosis and treatment. However, a lack of symptoms and signs and normal ALT levels does not exclude progressive damage in chronic hepatitis. Liver biopsy may be required in some patients, particularly in the context of chronic hepatitis B, and remains the definitive test to identify the stage of liver disease.

Many patients who are aware that they may have put themselves at risk of contracting HBV or HCV are reluctant to seek a diagnosis, not only because of fear of prejudice and hesitancy in facing a potential serious illness, but also because they are pessimistic about treatment outcomes. It is essential that clinicians present optimism, since in recent years there have been substantial gains in outcomes following treatment. Support groups such as State and Territory Hepatitis C Councils (Chapter 15) can be helpful in providing additional resources to help present a more optimistic view and give patients a better sense of control over this chronic condition.
<table>
<thead>
<tr>
<th>Investigation</th>
<th>Reason</th>
</tr>
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<tbody>
<tr>
<td>HCV antibody (anti-HCV)</td>
<td>Exposure to HCV.</td>
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<tr>
<td>Qualitative HCV RNA PCR</td>
<td>Detects presence of HCV.</td>
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<tr>
<td>Quantitative HCV PCR RNA viral load</td>
<td>Provides quantitative HCV viral load measurement.</td>
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<tr>
<td>HCV genotype</td>
<td>Predicts response and optimal duration of treatment.</td>
</tr>
<tr>
<td>HBsAg</td>
<td>Indication of natural hepatitis B infection. Occurs with acute infection and may disappear or persist indefinitely. Marker of ongoing infection.</td>
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<tr>
<td>Anti-HBs</td>
<td>Indication of immunity to hepatitis B (from natural infection or vaccination).</td>
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<tr>
<td>HBcAg</td>
<td>Found in the liver only and not usually measured.</td>
</tr>
<tr>
<td>Anti-HBc IgM</td>
<td>Marker of recent exposure to hepatitis B virus. Does not persist more than a year following acute infection.</td>
</tr>
<tr>
<td>HBeAg</td>
<td>Indication of hepatitis B viral replication and high infectivity. Useful serological marker in the investigation of a person who is found to be HBsAg+.</td>
</tr>
<tr>
<td>Anti-HBe</td>
<td>Indication of hepatitis B viral clearance and occurs following loss of HBeAg. May also occur in the presence of ‘pre-core mutant’ disease in association with abnormal ALT and elevated HBV DNA.</td>
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<tr>
<td>HBV DNA</td>
<td>Indication of viral replication. Quantitative level may help to predict response to antiviral treatment (higher levels associated with poorer outcome) and monitor response to treatment. Useful serological marker in the investigation of a person who is found to be HBsAg+.</td>
</tr>
<tr>
<td>ALT</td>
<td>Detection of abnormal ALT suggests antiviral treatment should be considered.</td>
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<tr>
<td>Albumin</td>
<td>Indication of synthetic liver function, i.e. low albumin indicates liver failure.</td>
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<tr>
<td>FBC</td>
<td>Platelet counts may be low due to the progression of fibrosis or portal hypertension.</td>
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<tr>
<td>INR</td>
<td>Indication of synthetic function.</td>
</tr>
<tr>
<td>HAV, HBV and HIV serology</td>
<td>To determine need for vaccination to prevent superinfection with HAV and HBV. Presence of HIV alters prognosis.</td>
</tr>
<tr>
<td>Thyroid function tests</td>
<td>To exclude associated thyroid disorder and as a baseline investigation prior to interferon treatment (which can cause toxicity).</td>
</tr>
<tr>
<td>Ferritin</td>
<td>To exclude haemochromatosis (may reflect severity of liver disease).</td>
</tr>
<tr>
<td>U&amp;E and creatinine</td>
<td>Baseline prior to treatment. To exclude possible renal involvement, i.e. glomerulonephritis.</td>
</tr>
<tr>
<td>Alpha-feto-protein</td>
<td>Baseline investigation for hepatocellular carcinoma.</td>
</tr>
<tr>
<td>Caeruloplasmin and copper</td>
<td>To exclude Wilson’s disease.</td>
</tr>
<tr>
<td>Alpha-1-antitrypsin</td>
<td>To exclude alpha-1-antitrypsin deficiency.</td>
</tr>
<tr>
<td>ANA, SMA, LKM</td>
<td>To exclude autoimmune disease.</td>
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<tr>
<td>Abdominal ultrasound</td>
<td>To assess liver and biliary tree and to screen for hepatoma. Can also be useful to detect small amounts of ascites.</td>
</tr>
<tr>
<td>Liver biopsy</td>
<td>May be required to assess severity of disease.</td>
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References