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Eliminating hepatitis C: Part 2. Assessing your patient for antiviral treatment

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Authors
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With the introduction of direct-acting antivirals (DAAs) in Australia in 2016, most people with chronic hepatitis C can be cured of this infection. GPs and suitably qualified nurse practitioners working in all areas of primary care have a key role in identifying, testing and treating their patients with hepatitis C.

The previous article in this series discussed how to identify your patients with hepatitis C. This article provides practical advice on assessing a patient after diagnosis in preparation for DAA therapy. This includes determining whether they can be safely treated in general practice or require specialist referral.

As soon as a patient is diagnosed with chronic hepatitis C, preparations can begin for treatment with direct-acting antivirals (DAAs). Most patients can receive DAA therapy in general practice. GPs are ideally placed to assess their patients in preparation for DAA therapy and to identify the minority who require specialist referral.

**KEY POINTS**

- Most patients with hepatitis C can be treated with direct-acting antivirals (DAAs) in general practice.
- GPs are ideally placed to assess patients in preparation for DAA therapy.
- Pretreatment assessment includes a comprehensive medical and social history, medication review, physical examination and investigations.
- Key questions to determine the safety of DAA therapy in primary care concern the presence of cirrhosis, hepatitis C virus (HCV) genotype, hepatitis B or HIV coinfection, potential drug interactions, previous HCV treatment and renal function.
- Patients with cirrhosis, complex comorbidities or who have previously failed DAA therapy should be referred for specialist care.
After diagnosis, what next?
All people diagnosed with hepatitis C should be considered for DAA therapy. DAAs have the potential to cure most people with hepatitis C and have few contraindications. As soon as a patient is diagnosed with hepatitis C, assessment for treatment can begin, in consultation with the patient.

Pretreatment assessment
Patient assessment in preparation for treatment includes:
- comprehensive medical and social histories
- medication review
- physical examination
- investigations, including a liver fibrosis assessment.

A full list of the required assessments and investigations appears in Box 1.

Six key questions need to be answered to help determine whether the patient can be treated safely in primary care or needs to be referred to a specialist, and the most appropriate treatment option. These questions regard the individual, the hepatitis C virus (HCV) and the liver. The key questions are:
- Does the patient have cirrhosis?
- What is the genotype of the infecting HCV? (This requirement may be removed in the future owing to the availability of pangenotypic agents.)

1. PRETREATMENT ASSESSMENT OF PEOPLE WITH CHRONIC HEPATITIS C VIRUS (HCV) INFECTION

<table>
<thead>
<tr>
<th>History</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Estimated duration of HCV infection</td>
</tr>
<tr>
<td>• Previous HCV treatment: date, regimen and response</td>
</tr>
<tr>
<td>• Cofactors for liver disease progression: alcohol intake, marijuana use, virological cofactors (HIV, hepatitis B virus), diabetes, obesity</td>
</tr>
<tr>
<td>• If ribavirin treatment is planned then note any history of ischaemic heart disease or cardiovascular risk factors</td>
</tr>
<tr>
<td>• Vaccinations against hepatitis A and B viruses</td>
</tr>
<tr>
<td>• Physical and psychiatric comorbidities</td>
</tr>
<tr>
<td>• Ongoing risk factors for viral transmission and reinfection</td>
</tr>
<tr>
<td>• Social issues, potential barriers to medication adherence</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Medication</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Concomitant medications (prescription, over the counter, illicit)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Physical examination</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Features of cirrhosis: hard liver edge, spider naevi, leukonychia</td>
</tr>
<tr>
<td>• Features of decompensation or portal hypertension: jaundice, ascites, oedema, bruising, muscle wasting, encephalopathy</td>
</tr>
<tr>
<td>• Body weight and body mass index</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Virology</th>
</tr>
</thead>
<tbody>
<tr>
<td>• HCV RNA PCR testing</td>
</tr>
<tr>
<td>• HCV genotype†</td>
</tr>
<tr>
<td>• Consider HCV RNA level (quantitative)‡</td>
</tr>
<tr>
<td>• Hepatitis B virus serology (HBsAg, anti-HBc, anti-HBs§), HIV, hepatitis A serology</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Investigations</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Full blood examination, liver function tests, urea and electrolytes, eGFR, INR</td>
</tr>
<tr>
<td>• Pregnancy test for women with childbearing potential</td>
</tr>
<tr>
<td>• Liver fibrosis assessment, for example</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
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<td></td>
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</tbody>
</table>

Abbreviations: anti-HBc = hepatitis B core antibody; anti-HBs = hepatitis B surface antibody; APRI = aspartate aminotransferase to platelet ratio index; DAA = direct-acting antiviral; eGFR = estimated glomerular filtration rate; ELF = enhanced liver fibrosis; HBsAg = hepatitis B surface antigen; INR = international normalised ratio.

† HCV genotyping is a PBS criterion; it is important before prescribing elbasvir plus grazoprevir or sofosbuvir plus ledipasvir.
‡ HCV RNA level is important for determining eligibility for eight-week treatment duration with sofosbuvir plus ledipasvir.
§ All three tests for hepatitis B virus may be requested if the clinical notes indicate acute or chronic hepatitis.
¶ FibroGENE is a gene-based model for staging liver fibrosis; a FibroGENE calculator is available online (www.fibrogene.com/viral_hepatitis.html).
Is the patient coinfected with HIV or hepatitis B virus (HBV)?

Are there any potential drug interactions between the patient’s current medication and the DAAs?

Has the patient previously been treated for hepatitis C?

What is the patient’s renal function?

An important part of the pretreatment assessment is determining the presence of advanced liver disease. Patients with cirrhosis require specialist referral and may need changes to the standard treatment regimen.

It is also important to address potential psychosocial barriers to treatment during the assessment process. Current active injecting drug use is not a contraindication to hepatitis C treatment. However, some patients may need support to stabilise drug and alcohol use or to establish adherence support services before treatment.

Vaccinations

All susceptible patients with hepatitis C should be offered vaccinations against hepatitis A and B viruses. These vaccinations are subsidised for patients with liver disease and those who are at high risk of infection in some jurisdictions.

Liver fibrosis assessment

Liver fibrosis assessment is important to determine whether the patient has cirrhosis (Flowchart). Although all patients are eligible for treatment, regardless of their cirrhosis status, the presence of cirrhosis determines the need for referral for specialist care and influences treatment regimen and duration in some cases, as well as follow up after treatment. Most patients do not have advanced liver disease and can be treated easily in primary care.

The two most widely used noninvasive methods for assessing liver fibrosis are:

- the aspartate aminotransferase (AST) to platelet ratio index (APRI)
- transient elastography, including FibroScan.

Current active injecting drug use is not a contraindication to hepatitis C treatment

AST to platelet ratio index

The APRI has been developed as a simple serum biomarker for assessing fibrosis using results from a full blood count and liver function test. The APRI is calculated from the AST level and platelet count.

It is calculated using the formula shown in the Flowchart. An APRI result of 1.0 or more indicates possible cirrhosis; the patient should be referred for further assessment including transient elastography. An APRI result less than 1.0 suggests that cirrhosis is unlikely and further evaluation for cirrhosis is usually not necessary unless clinically indicated; the patient can proceed on the treatment pathway.
Transient elastography

Transient elastography measures the stiffness of the liver, which is used to assess liver fibrosis. Threshold levels can determine the presence of cirrhosis. FibroScan is the most extensively validated and widely available method of transient elastography. It uses a series of short, pulsed, low-frequency sound waves and is similar to an abdominal ultrasound examination in terms of patient experience. FibroScan takes a trained operator (usually a nurse or doctor) 10 to 15 minutes to perform. GPs can refer patients to a liver clinic for a FibroScan. In some areas, specialist hepatology nurses offer FibroScan clinics in the community.

A FibroScan reading of 12.5 kPa or higher indicates a high likelihood of cirrhosis. The patient requires referral to a specialist for management and regular monitoring for complications of cirrhosis, including hepatocellular carcinoma. Patients with a FibroScan result of less than 12.5 kPa are generally suitable for DAA therapy in primary care.

**A FibroScan reading of 12.5 kPa or higher indicates a high likelihood of cirrhosis. The patient requires referral to a specialist**

Alternative methods for evaluating liver stiffness are offered by some radiology services as an add-on to a liver ultrasound examination. They include shear wave elastography and acoustic radiation force impulse (ARFI) imaging. These methods are convenient but less well validated in identifying fibrosis in the presence of chronic hepatitis C.¹

**Risk factors and signs of cirrhosis**

Other clinical information should be collected to determine a patient’s risk of cirrhosis. This includes their clinical risk factors for cirrhosis and signs of advanced liver disease on physical examination (Box 2). A comprehensive patient assessment is needed because the APRI and FibroScan may not detect cirrhosis in all patients.

**Drug interactions**

DAAs can interact with many medications. Common examples include proton pump inhibitors, statins, ethinylestradiol and antiepileptic medications such as carbamazepine and phenytoin. The potential for interactions depends on the specific DAA. The University of Liverpool in the UK has developed a comprehensive tool for checking potential drug interactions (available online at: www.hepdruginteractions.org).

**When to refer**

Most patients with hepatitis C can receive DAA therapy safely in primary care (see the case study in Box 3 and the Table). Patients with cirrhosis, complex comorbidities or who have received previous failed DAA therapy should be referred for specialist care (Box 4).¹²

Appropriate specialists are those who have expertise in treating patients with viral hepatitis. This includes gastroenterologists, hepatologists, infectious diseases physicians and sexual health physicians, depending on the indication for the referral and local pathway (including telehealth or other videoconferencing consultations for GPs and patients in rural or remote areas who have limited access to specialist care).

**Psychosocial assessment**

When determining patient readiness for DAA therapy, GPs must take account of comorbidities, lifestyle and social issues. Major psychiatric disorders such as schizophrenia or ongoing drug use (including injecting drug use) and alcohol use or being homeless can pose challenges to adherence for patients but are not contraindications to treatment. It is important to optimise the patient’s health when they are considering treatment.

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**Figure.** Formula for the aspartate aminotransferase (AST) to platelet ratio index (APRI).

\[
\text{APRI} = \frac{\text{AST level (IU/L)}}{\text{AST upper limit of normal (IU/L)}} \times \frac{\text{Platelet count (10⁹/L)}}{100}
\]

**2. RISK FACTORS FOR CIRRHOSIS AND SIGNS OF ADVANCED LIVER DISEASE**

**Clinical risk factors for cirrhosis**¹

- Male sex
- Older age when infected
- More than 20 years of HCV infection
- Comorbidities including:
  - diabetes
  - metabolic syndrome
  - coinfection with hepatitis B virus or HIV
  - obesity
  - excessive alcohol consumption

**Physical signs of advanced liver disease**

- Leukonychia
- Spider naevi
- Palmar erythema
- Gynaecomastia
- Hepatic flap
- Foetor
- Splenomegaly or hepatomegaly
- Oedema
- Ascites
- Jaundice
- Encephalopathy

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**Box 1: Pre-treatment evaluation**

**Box 2: Physical signs of advanced liver disease**

**Box 3: Pre-treatment assessment**

**Box 4: Psychosocial assessment**

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**Box 5: Drug interactions**

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**Box 6: When to refer**

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**Box 7: Psychosocial assessment**

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**Box 8: Other clinical information**

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**Box 9: Clinical risk factors for cirrhosis**

---

**Box 10: Physical signs of advanced liver disease**

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**Box 11: Drug interactions**

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**Box 12: When to refer**

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**Box 13: Psychosocial assessment**

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**Box 14: Other clinical information**

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**Box 15: Clinical risk factors for cirrhosis**

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**Box 16: Physical signs of advanced liver disease**

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**Box 17: Drug interactions**

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**Box 18: When to refer**

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**Box 19: Psychosocial assessment**

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**Box 20: Other clinical information**

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**Box 21: Clinical risk factors for cirrhosis**

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**Box 22: Physical signs of advanced liver disease**

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**Box 23: Drug interactions**

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**Box 24: When to refer**

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**Box 25: Psychosocial assessment**

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**Box 26: Other clinical information**

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**Box 27: Clinical risk factors for cirrhosis**

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**Box 28: Physical signs of advanced liver disease**

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**Box 29: Drug interactions**

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**Box 30: When to refer**

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**Box 31: Psychosocial assessment**

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**Box 32: Other clinical information**

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**Box 33: Clinical risk factors for cirrhosis**

---

**Box 34: Physical signs of advanced liver disease**

---

**Box 35: Drug interactions**

---

**Box 36: When to refer**

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**Box 37: Psychosocial assessment**

---

**Box 38: Other clinical information**

---

**Box 39: Clinical risk factors for cirrhosis**

---

**Box 40: Physical signs of advanced liver disease**

---

**Box 41: Drug interactions**

---

**Box 42: When to refer**

---

**Box 43: Psychosocial assessment**

---

**Box 44: Other clinical information**

---

**Box 45: Clinical risk factors for cirrhosis**

---

**Box 46: Physical signs of advanced liver disease**

---

**Box 47: Drug interactions**

---

**Box 48: When to refer**

---

**Box 49: Psychosocial assessment**

---

**Box 50: Other clinical information**

---

**Box 51: Clinical risk factors for cirrhosis**

---

**Box 52: Physical signs of advanced liver disease**

---

**Box 53: Drug interactions**

---

**Box 54: When to refer**

---

**Box 55: Psychosocial assessment**

---

**Box 56: Other clinical information**

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**Figure.** Formula for the aspartate aminotransferase (AST) to platelet ratio index (APRI).
3. CASE STUDY: A NEW PATIENT WITH A HEPATITIS C RISK FACTOR

Michelle is a fit and active woman aged 49 years who recently transferred to your practice because her previous GP retired. In your initial consultation, you take a medical history, including Michelle’s current medications. She has asthma and mild gastric reflux. Her current medications include budesonide/formoterol fumarate dihydrate 200/6 two inhalations twice daily, salbutamol as required and methadone 40 mg daily.

You start a conversation with Michelle about her methadone treatment. She reports that she injected heroin between the ages of 14 and 35 years. She commenced methadone treatment when she was 35 and has not injected drugs for the past 10 years. She has no current or past history of significant alcohol use. You ask if she has ever been tested for hepatitis C and she reports that a previous GP told her she had been exposed to the virus but she is unsure if she has a current infection. She has not previously received antiviral therapy.

You order a comprehensive set of pathology investigations. The results show that Michelle has current hepatitis C with elevated aspartate aminotransferase (AST) and alanine aminotransferase levels (Table).

You calculate Michelle’s AST to platelet ratio index (APRI) score using her AST and platelet levels:

\[
APRI = \left( \frac{53}{40} \right) / 255 \times 100 = 0.52.
\]

An APRI of 0.52 indicates a low likelihood of cirrhosis. Michelle has evidence of past cleared hepatitis B virus (HBV) infection but is not currently coinfected with HBV or HIV. She has normal renal function and has not been previously treated for hepatitis C. You decide that it is appropriate for Michelle to receive antiviral treatment in primary care.

Treatment and monitoring will be covered in the next article in this series.

### TABLE. MICHELLE’S TEST RESULTS

<table>
<thead>
<tr>
<th>Test</th>
<th>Result (reference range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AST (U/L)</td>
<td>53 (&lt;40)</td>
</tr>
<tr>
<td>ALT (U/L)</td>
<td>60 (&lt;40)</td>
</tr>
<tr>
<td>Bilirubin (mcmol/L)</td>
<td>20 (4 to 20)</td>
</tr>
<tr>
<td>Platelets (x 10⁹ cells/L)</td>
<td>255 (150 to 400)</td>
</tr>
<tr>
<td>eGFR (mL/min/1.7 m²)</td>
<td>97 (&gt;90)</td>
</tr>
<tr>
<td>HCV RNA</td>
<td>Viral load 3,100,000 IU/mL, genotype 3</td>
</tr>
<tr>
<td>Hepatitis B serology</td>
<td>Anti-HBs and anti-HBc positive, HBsAg negative</td>
</tr>
<tr>
<td>HIV</td>
<td>Negative</td>
</tr>
<tr>
<td>Hepatitis A total antibody</td>
<td>Negative</td>
</tr>
<tr>
<td>Pregnancy test</td>
<td>Negative</td>
</tr>
<tr>
<td>Full blood count, urea and electrolytes, INR, fasting glucose level, body mass index</td>
<td>Within reference range</td>
</tr>
</tbody>
</table>

Abbreviations: ALT = alanine aminotransferase; anti-HBs = hepatitis B surface antibody; anti-HBc = hepatitis B core antibody; anti-HBs = hepatitis B surface antibody; AST = aspartate aminotransferase; eGFR = estimated glomerular filtration rate; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; INR = international normalised ratio.

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This may include initiating opioid substitution therapy before starting treatment and referral to support services as required.

More intensive adherence support may need to be organised before treatment. This will be covered in more detail in the next article in the series.

Conclusion
The role of GPs in managing patients with hepatitis C and preparing them for DAA treatment is crucial to the hepatitis C elimination effort in Australia. Resources on hepatitis C management for healthcare providers and patients are shown in Box 5. If left untreated, people with hepatitis C will be at increased risk of developing cirrhosis and associated complications, including liver failure and hepatocellular carcinoma. Preparation for hepatitis C treatment involves a few straightforward steps. Most people diagnosed with hepatitis C can be assessed and treated in primary care, giving GPs an exciting opportunity to offer their patients a cure.

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References

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