Australian Government
Department of Home Affairs

Notes for Guidance for viral hepatitis

Deals with financial implications and consideration of prejudice of access to services associated with viral hepatitis

July 2019

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Information provided in this document, including the estimated financial considerations within a specified framework for treatment, are based on accurate, available resources at the time of development/review. It is the end user's responsibility to re-confirm the details before using the information for any binding purposes. This includes consideration of the current eligibility criteria and cost of medications set out in the Pharmaceutical Benefits Scheme (PBS) tables, where there have been significant changes that would affect the outcome (for which archived tables can be accessed via the following link: http://www.pbs.gov.au/info/publication/schedule/archive#_2003).

Hepatitis A

Definition and brief description of hepatitis A

Hepatitis A is the most common form of acute viral hepatitis in the world. Hepatitis A accounts for a significant number of cases of clinical illness annually in Australia, and approximately 40% of older adults are likely to have evidence of past hepatitis A virus (HAV) infection. Contaminated stool is the primary source of transmission and enteric transmission by person-to-person contact is the predominant way of spreading the disease. Large families, household crowding, poor education, inadequate human waste disposal, mixing with other children in day-care centres and male homosexual activity are all associated with an increased likelihood of hepatitis A infection.

Hepatitis A cases should be notified to the Commonwealth's National Notifiable Diseases Surveillance System (NNDSS).[6]

Prognosis, including rate of progression

Hepatitis A is usually a mild disease, particularly in children, in whom it is frequently asymptomatic. Middle-aged and older people and those with underlying liver disease are more likely to have a more severe clinical illness, which resolves with symptomatic management. Fulminant hepatitis is a rare complication of hepatitis A. There is no chronic carrier state for hepatitis A (unlike hepatitis B or hepatitis C), although approximately 15% of people infected with HAV are likely to have a prolonged period of jaundice or a relapsing illness, which is usually associated with complete recovery.

Information required

The diagnosis of acute hepatitis A is made by the identification of immunoglobulin M (IgM) antibodies to HAV (anti-HAV) in the serum. This is usually accompanied by the assessment of liver function tests, a coagulation profile, blood tests to exclude other causes of acute hepatitis and an abdominal ultrasound examination.

Currently accepted treatments

There is no specific treatment for acute hepatitis A. Passive immunisation with human Ig containing IgG anti-HAV is recommended for post-exposure prophylaxis and provides protection against clinical hepatitis in 80–90% of the recipients if given within 6 days of exposure. Several inactivated HAV vaccines have been developed in the last 10 years and these are highly effective with 95–100% protective efficacy in healthy individuals.

Financial considerations

The cost of HAV will not represent a significant cost.

Prejudice to access and scarcity of resources

With reference to 'Sch4/4005-4007 – The Health Requirement' dated July 2019 on the health-related criteria, none of the services considered short in supply are applicable to HAV.

Effect on applicant's ability to work

Adult patients with acute hepatitis A are likely to require a period of absence from their usual employment. The duration of this period will vary depending on the severity of the illness, the clinical course of the infection and the underlying general health of the individual.

Hepatitis B

Definition and brief description of hepatitis B[1,8]

Hepatitis B virus (HBV) is a DNA virus that may cause inflammation of the liver, cirrhosis, liver failure and liver cancer. The virus is transmitted by contact with the blood or body fluids of an infected person. The infection is vaccine-preventable.

A patient is said to have chronic hepatitis B (CHB) when the acute infection persists beyond 6 months. Symptoms of CHB are often mild and non-specific until the emergence of features of hepatic decompensation.

CHB infection causes an increased risk of permanent liver injury, including cirrhosis and liver cancer.

Despite universal infant vaccination programs, the burden of disease attributable to CHB continues to be significant for several reasons, such as the long delay between initial infection and the onset of complications and the large number of existing chronic infections.

In Australia, about 7,000 new cases of CHB are diagnosed annually. This estimate is, however, only about half of those living with the infection. Majority of the new cases are attributable to migration and cannot be prevented through local vaccination initiatives. Hepatitis B cases should be notified to the Commonwealth's NNDSS.[6]

Prognosis and factors affecting progression, including rate of progression

Most cases of acute HBV infection acquired in adulthood resolve spontaneously without treatment.

The epidemiology of CHB is predominantly determined by the age at exposure, with about 90% of HBV-infected infants progressing to chronic infection, compared with only 5% of immunocompetent adults.

Table 1: *Chronic hepatitis B: Risk of progression*

Description	Perinatal	Childhood	Adult
Risk of development of chronic infection	80–90%	30%	< 5%
Risk of advanced liver disease (% exposed to HBV)	20–30%	5–10%	1–2%
Risk of advanced liver disease (% of those with chronic liver disease)	20–30%		

Source: Australian Society of HIV, Viral Hepatitis and Sexual Health Medicine (ASHM) guide: B Positive (Table 4.2; Chapter 4).[1] Available from: www.ashm.org.au/products/product/1976963310

Spontaneous viral clearance is much less common if HBV infection occurs at a younger age: 25% of those infected as infants and 90% of those infected at birth will not clear the virus, remain infectious and are at risk of developing chronic liver disease, cirrhosis and hepatocellular carcinoma (HCC).[1,8]

The host immune response targeted against infected liver cells is the underlying mechanism by which liver damage occurs in patients with CHB.

The natural course of CHB is extremely variable in terms of the level of viral replication, the extent of inflammatory activity in the liver and the likelihood of progression to cirrhosis and HCC.[1,8]

Patients with chronic HBV infection can exist in either a high replicative state (high HBV DNA) or a low replicative state (low HBV DNA). The risk of cirrhosis and HCC increases with increasing gradient across HBV DNA levels. However, infection can switch from a non-replicative state to a highly replicative state, and this is a particular risk in patients undergoing chemotherapy or being treated with immunosuppressive medications.

People at risk of CHB include migrants born in regions endemic (> 2% prevalence) for HBV – that is the Asia–Pacific regions. Other Australian-born individuals at higher risk for CHB include those whose parents born overseas in an endemic area, as well as those exposed to HBV through sexual contact or medical transmission before routine blood donor screening.[1,8]

Complications such as cirrhosis, liver failure and liver cancer (specifically, HCC) result into deaths in up to 25% of people living with CHB. All complications can be minimised through antiviral therapy.[1,8]

Information required

Screening for HBV

Based on the National HBV Testing Policy, routine CHB screening is recommended in the following populations:[1,8]

- people born overseas in Asian or Pacific regions
- people living with human immunodeficiency virus (HIV) and/or hepatitis C virus (HCV)
- people who inject drugs
- people who are undergoing dialysis
- people who have ever been in custodial settings
- people with haemophilia/history of blood transfusion in the pre-screening era
- men who have sex with men
- sex workers
- people with multiple sexual partners
- household and sexual contacts of people with CHB.

Diagnosis of hepatitis B infection

Acute hepatitis B infection: The diagnosis of acute hepatitis B is based on medical history, physical examination, elevated liver enzymes and positive serological markers – hepatitis B surface antigen (HBsAg) and antibody to hepatitis B core antigen (anti-HBc) immunoglobulin M (IgM). These tests are repeated monthly after the initial diagnosis to ensure seroconversion and viral clearance.[1,8]

CHB infection: The diagnosis of CHB can be difficult because symptoms are often mild and non- specific. CHB is marked by ongoing serological evidence of infection and variable liver inflammation. The persistence of HBsAg for longer than 6 months has traditionally defined the presence of CHB infection.[1,8]

Further testing

Once a patient has been identified with a persistently positive HBsAg, a series of tests are usually performed to establish the viral load, serology, level of liver inflammation, extent of liver fibrosis, presence/absence of HCC and other underlying liver diseases. These tests include:[1,8]

- full blood count (FBC) with platelets and coagulation profile
- liver function tests

- complete HBV serology including hepatitis B e antigen (HBeAg), antibody to HBeAg (anti-HBeAg) and HBV DNA measurement
- tests for co-infection with other viruses, such as HCV, hepatitis D virus (HDV), HIV, and tests for other causes of liver disease
- ultrasound to screen for HCC
- serum alpha-fetoprotein (AFP)
- liver biopsy – though this is rarely necessary; however, clinicians may consider requesting a biopsy in order to differentiate the cause of liver injury in patients with more than one possible liver disease
- liver stiffness measured by transient elastography (FibroScan®) – this is a non-invasive method to determine the extent of hepatic fibrosis and for monitoring liver disease progression. It is not reimbursed through Medicare for diagnosis and staging of CHB.

Determination of HBV genotype is not currently recommended as a routine measure, as there are presently insufficient data to suggest that it significantly alters decisions regarding choice of therapy. However, this position may change as more data emerge on the specific genotypes.

Monitoring patients with diagnosed HBV infection

Patients without evidence of active liver disease should be monitored on a regular basis and have an alanine aminotransferase (ALT) measurement performed at least every 6 months.

The frequency of monitoring during treatment depends upon the chosen antiviral therapy. (See *Currently accepted treatments* section below).

For patients using pegylated interferon (PEG-IFN), FBC should be performed on a fortnightly basis until cell counts are stable, after which the frequency of testing can be reduced to monthly. Liver function tests should be performed in conjunction with the FBC. HBV serology should be checked every 3 months and HBV DNA assessed every 3–6 months.

For patients using oral antiviral therapy, ALT should be measured every 3 months. HBV DNA should be checked every 3 months during the early phases of therapy if the chosen agent has a high rate of resistance, or if the treated patient has a significant risk of liver decompensation should a resistant HBV strain emerge. HBV DNA can be checked every 6 months once a state of undetectable HBV DNA has been achieved and if the antiviral therapy has a demonstrated low risk of resistance.

Patients with CHB and a high risk of HCC (such as male gender, family history of HCC, older age, the presence of cirrhosis and HCV co-infection) should undergo surveillance every 6 months using liver imaging and serum (AFP) measurement.[1,8]

For recommended treatment duration see *Currently accepted treatments* section below.

Currently accepted treatments

Types of drugs

Direct antiviral agents

Acute HBV is usually self-limiting and is not treated. However, oral antiviral therapy should be considered in patients who develop severe hepatitis as they are at risk of acute liver failure; although this treatment strategy has not been subjected to a controlled clinical trial.

CHB infection with low viraemia: Normal liver function tests are monitored on a regular basis and do not require antiviral therapy.[1,8]

CHB infection with significant viraemia and evidence of ongoing liver inflammatory activity is treated with PEG-IFN or oral antiviral therapy.

Tenofovir and entecavir have high barriers to resistance and have become the preferred first-line therapies in CHB. Treatment in the majority of patients is likely to be lifelong. These medications are well tolerated without significant side effects in most patients

Preference of drugs is largely determined by individual clinician choice, patient response including renal health, pregnancy and fertility concerns, and the development of any drug resistance. Rather than ALT or VL, likelihood of fibrosis or cirrhosis is the key determinant of long-term outcomes. That is why, these treatments are not approved in children.

Lamivudine is utilised as a preventive antiviral during chemotherapy or immunotherapy to prevent the re-emergence of HBV in low risk patients identified as to be in the immune control phase of the infection.

Entecavir is not recommended in pregnancy. It should also not be used in lamivudine-refractory patients. Tenofovir may cause or exacerbate decreased bone mineral density. It is best to be avoided in osteoporotic patients.

Tenofovir is also is used in combination with other antivirals to treat HIV. It has been used successfully in pregnancy for HIV and HBV without maternal or foetal complications. Its dosage has to be adjusted in patients with renal impairment. Entecavir is a better option in HIV-positive patients, as well as in those with significant diabetes or hypertension who may be at risk of kidney damage.

Adefovir is no longer used on its own due to the high rates of viral resistance; tenofovir and entecavir are listed as Section 100 drugs as first-line therapy for patients with chronic HBV with appropriate viral loads.

Tenofovir and entecavir are also listed for patients who have developed resistance to other oral agents. PBS subsidy requires compliance with the clinical criteria as given in Table 3.

PEG-IFN

PEG-IFNs are administered by injection and may offer alternative options when finite therapy is desired, such as in young patients. Pegylated forms of IFN are preferred over the non-pegylated forms due to weekly dosing and possibly improved efficacy, although the side effects are similar. [1,8]

Not all patients with CHB are suitable to receive PEG-IFN, especially if with decompensated cirrhosis. Young patients with high ALT, low viral load and infection with wild-type CHB are more likely to respond to PEG-IFN.

PEG-IFNs have a restricted listing on the Pharmaceutical Benefits Scheme (PBS), with a lengthy treatment course of 48 weeks, accompanied with many side effects, including bone marrow depression, influenza-like symptoms and neuropsychological side effects. The treatment is typically not successful in achieving SVR in 80-90% of patients commenced on therapy.

Duration of treatment[1,8]

Duration of treatment will depend on patient's viral load, other serological responses and clinical status, particularly the development of cirrhosis. For patients with CHB infection with significant viraemia and evidence of ongoing liver inflammatory activity, treatment with oral antiviral therapy is likely to be lifelong, particularly in HBeAg-negative patients, unless they achieve HBsAg loss or seroconversion.

Complete viral eradication is rarely achieved. Hence, the aim of therapy is biochemical control (normalisation of ALT) and virologic control (< 2,000 IU/mL for IFN treatment and undetectable virus for direct antiviral therapy). Ideally, this control should be sustained when the patient has ceased therapy; however, when using direct antiviral therapy, long-term maintenance treatment is likely to be required in the majority of patients.

All patients who discontinue treatment must be monitored closely for a relapse. Relapse rates are high (up to 50%); therefore, once commenced on treatment, the majority of patients are likely to require very prolonged or lifelong treatment.

HBeAg-positive patients: Oral antivirals may be stopped (with the help of nucleos(t)ide analogues) after a sustained period of seroconversion and undetectable HBV. Most guidelines recommend a 612 month consolidation period before stopping therapy. Nevertheless, some patients will relapse after treatment is stopped and develop symptoms. Check for relapse at 3 months after treatment is stopped.

The longer the period of consolidation after the HBeAg seroconversion and before cessation of therapy, the less likely the patient is to relapse. In HBeAg-positive cases with a sustained HBeAg seroconversion to anti-HBe, cessation of oral treatment may be possible. Such cases are not clearly defined but are most likely to:

- be non-cirrhotic
- have been treated, with a consolidation period of at least 12 months with persistently undetectable serum HBV DNA and normal ALT
- not suffer from another form of immunocompromise (e.g. HIV infection, haematological malignancy, autoimmune disease requiring pharmacological immunosuppression)
- not prefer to take lifelong therapy.

However, it should be stressed that there is a good deal of unknowns in all of the above and no strong clinical recommendation can be made, leaving the clinical decision still somewhat discretionary. Treatment with oral nucleos(t)ide analogues is likely to be continued lifelong in the vast majority of patients (95%).[8]

HBeAg-negative patients: the risk of virologic relapse after stopping therapy is high and patients are likely to continue lifelong therapy unless they lose HBsAg positivity, which is not common (< 5%).

Table 2: Chronic hepatitis B: Summary of efficacy data with treatments

Drug	Duration of treatment	HBeAg seroconversion rate (%)	Patients with HBV DNA undetectable (at 1 year) (%)*
Lamivudine	1 year 3 years	18 40	40–44
Entecavir	1 year 3 years	21 39	67
Adefovir	1 year 3 years	18 43	21
Tenofovir	1 year 3 years	21 NA	76
PEG-IFN	48 weeks	27	37
*Not head-to-head trials; different patient populations and trial designs. IFN and lamivudine: hybridisation assay; adefovir, entecavir and PEG-IFN: polymerase chain reaction (PCR) assay.			
Source: GESA CHB recommendations (Table 7).[8] Available from: www.gesa.org.au/resources/clinical-guidelines-and-updates/chronic-hepatitis-b/			

Financial considerations

Table 3 summarises the commonly prescribed medications for CHB treatment.[8]

Prejudice to access and scarcity of resources

End-stage liver disease (ESLD) associated with HBV (about 5%) is an indication for liver transplantation. With reference to 'Sch4/4005-4007 – The Health Requirement' dated July 2019 on the health-related criteria, liver transplantation has been identified to be short in supply.

Refer to section below on *Liver transplantation*.

Effect on applicant's ability to work

Adult patients with acute HBV are likely to require about 2-4 weeks of absence from their usual employment. The duration of this period will vary depending on the severity of the illness, the clinical course of the infection and the underlying general health of the individual.

Adult patients with CHB usually carry on with their usual employment until the onset of limiting symptoms of their underlying disease.

Table 3: *Chronic hepatitis B: Costs of commonly prescribed medications as of April 2019*

Drug	PBS code	PBS criteria*		Usual dose/ frequency	Unit cost	Estimated annual cost
		With cirrhosis	Without cirrhosis			
Tenofovir disoproxil fumarate 300 mg tablet, 30	10310P	(1,2,6,7) OR (1,2,9,10)	(5,6,7) OR (3,4,9,10)	300 mg daily	$404.59	$5,260
Entecavir 500 microgram tablet, 30	10279B	(1,2)	(3,4)	0.5 mg oral once daily (often extended therapy)	$179.25	$2,330
Entecavir 1 mg tablet, 30	10353X	(1,2,8)	(5,8)	1.0 mg oral once daily (usually lifelong)	$289.22	$3,760
Lamivudine 100 mg tablet, 28	10315X	(1,2)	(3,4)	100 mg once daily (often extended therapy)	$40.35	$565
Lamivudine 10 mg/mL oral liquid, 240 mL	10320E	(1,2)	(3,4)	Maximum 100 mg (10 mL) daily	$59.13	$946
Adefovir dipivoxil 10 mg tablet, 30	10290N	(1,2,6)	(5,6)	10 mg once daily (usually lifelong)	$449.02	$5,837

Drug	PBS code	PBS criteria*		Usual dose/ frequency	Unit cost	Estimated annual cost
		With cirrhosis	Without cirrhosis			
PEG-IFN-alfa-2a 180 microgram/0.5 mL injection, 4 x 0.5 mL syringes	11037X	(1,2,10)	(3,4,10,11)	180 microgram SC once a week (only 1 course of 48 weeks)	$1,272.27	$15,267

SC: subcutaneous

*Eligibility criteria for PBS subsidy

1. Have detectable HBV DNA.
2. Those with Child's class B or C cirrhosis (ascites, variceal bleeding, encephalopathy, albumin < 30 g per litre, bilirubin > 30 micromoles per litre) should have their treatment discussed with a transplant unit prior to initiating therapy.
3. Evidence of chronic liver injury as determined by confirmed liver biopsy or elevated serum ALT (>30 U/L in men; >19 U/L in women)[1, 8]
4. In conjunction with documented CHB infection:
   a. if HBeAg positive – elevated HBV DNA levels > 20,000 IU/mL (100,000 copies/mL), OR
   b. if HBeAg negative – Elevated HBV DNA levels > 2,000 IU/mL (10,000 copies/mL).
5. Either of:
   a. repeatedly elevated serum ALT levels while on concurrent antihepadnaviral therapy of greater than or equal to 6 months duration, in conjunction with documented CHB infection; OR
   b. repeatedly elevated HBV DNA levels one log greater than the nadir value, or failure to achieve a 1 log reduction in HBV DNA within 3 months whilst on previous antihepadnaviral therapy, except in patients with evidence of poor compliance.
6. Failed antihepadnaviral therapy.
7. May receive treatment in combination with lamivudine, but not with other PBS-subsidised antihepadnaviral therapy.
8. Failed lamivudine therapy.
9. Nucleos(t)ide analogue naïve.
10. The treatment must be the sole PBS-subsidised therapy for this condition.
11. Not have previously received PEG-IFN-alfa therapy for the treatment of HBV.

Source of unit cost data: Schedule of Pharmaceutical Benefits – effective 1–30 April 2019.[5] Available from: www.pbs.gov.au/info/publication/schedule/archive

Unit cost of drug = Dispensed Price for Maximum Quantity (DPMQ)/Max qty packs.

Unit values are presented up to 2 decimal places. Total costs have been computed on these unit values, and rounded to the nearest whole number of full pack size costs.

Table 4: Chronic hepatitis B: MBS and other medical service costs as of April 2019

Service	MBS item	Frequency	Unit cost	Estimated annual cost
Medical				
GP consultation	23	2 per year	$37.60	$75
Specialist consultation – Treatment and management plan	132	Once per year	$267.85	$268
Specialist consultation – Subsequent consults for patient with 2 or more comorbidities	133	3 per year	$134.10	$402
Specialist consultations – Subsequent consults if no comorbidities	116	3 per year	$76.65	$230
Diagnostic & monitoring investigations				
HBV serology (complete)	69484	Every 3 months on therapy	$17.10	$68
HBV DNA	69482	Every 3–6 months on therapy	$152.10	$608
HBsAg	69481	Initial diagnosis and until acute infection resolves	$40.55	$122
HBeAg	69475	Initial diagnosis	$15.65	$16
HBeAg and anti-HBc IgM, anti-HCV, anti-HDV	69478	3-monthly intervals	$29.25	$117
Anti-HCV, anti-HDV		Initial assessment		
FBC – liver function test	66512	Initial assessment (5 or more tests per request)	$17.70	$18
Coagulation profile	65120	Initial assessment	$13.70	$14
HIV status	69384	Initial assessment	$15.65	$16
ALT	66500	Initial diagnosis, every 4 months in CHB	$9.70	$39
AFP	66650	Every 6 months if CHB	$24.35	$49
Bone densitometry (in presence of chronic liver disease)	12315	Annual	$102.40	$102
Ultrasound	55037	Every 6 months if CHB	$37.85	$76

Service	MBS item	Frequency	Unit cost	Estimated annual cost
Anaesthesia for liver biopsy	20702	Anaesthesia for percutaneous liver biopsy	$79.20	$79
Liver biopsy (assume percutaneous needle biopsy)	30409	Initial diagnosis	$174.45	$174

Source of unit cost data: Medicare Benefits Schedule (MBS) operating from 01 April 2019.[4] Available from: www.health.gov.au/internet/mbsonline/publishing.nsf/Content/downloads

Unit values are presented up to 2 decimal places. Total costs have been computed on these unit values, and rounded to the nearest whole number.

Hepatitis C

Definition and brief description of hepatitis C

HCV causes liver inflammation and may result in progressive liver injury, cirrhosis and HCC. Most patients with HCV have a history of intravenous drug use.

HCV is not vaccine-preventable. Hepatitis C cases should be notified to the Commonwealth's NNDSS.[6]

Prognosis and factors affecting progression, including rate of progression

HCV infection involves an initial (acute) phase of infection, which is usually asymptomatic. During this phase of the illness there is a rapid increase in viral levels, which is followed by the production of HCV antibodies by the host's immune system.

In general, 25% of people infected with HCV are likely to clear the virus within 1 year. Those that do not clear are described as having chronic hepatitis C (CHC). If left untreated, the outcomes are variable; for example, after 20 years of infection, approximately 7% of patients may develop liver cirrhosis, increasing to 20% after 40 years. After 40 years of infection, about 5% may develop liver failure or liver cancer.[2]

In patients with persistent infection, progression to liver disease is more frequent in those who:[10]

- are male
- have elevated ALT levels
- have heavy alcohol intake
- have evidence of obesity/metabolic syndrome
- acquired the infection at an older age
- have had infection for at least 40 years
- are co-infected with HBV or HIV.

Among patients who become HCV ribonucleic acid (RNA)-negative during treatment, some will relapse when therapy is stopped. A response is considered 'sustained' if HCV RNA remains undetectable for 6 months or more after stopping therapy.

The indications that a patient may be progressing from a state of compensated cirrhosis to liver failure are listed below.

- Subtle features
  - Hard liver edge and/or splenomegaly on physical examination
  - Mild thrombocytopaenia
  - Slightly low albumin
  - Slightly prolonged international normalised ratio (INR), nodular liver on computed tomography (CT)/ultrasound scans.
- Signs of progression to liver failure
  - Ascites, significantly low albumin

- Muscle wasting
- Hepatic encephalopathy
- Upper gastrointestinal bleeding from oesophageal/gastric varices or portal hypertensive gastropathy
- Hypersplenism (thrombocytopaenia, leukopenia).

Severity of cirrhosis is defined by the Child–Pugh criteria, as given in Table 5.

Refer to section: *Liver transplantation* below.

***Table 5:** Modified Child–Pugh criteria*

Parameters	1 point	2 points	3 points
Ascites	Absent	Slight	Moderate to severe
Bilirubin	< 2 mg/dL (< 34.2 micromol/L)	2–3 mg/dL (34.2–51.3 micromol/L)	> 3 mg/dL (> 51.3 micromol/L)
Serum albumin (g/L)	> 3.5 g/dL (35 g/L)	2.8–3.5 g/dL (28–35 g/L)	< 2.8 g/dL (< 28 g/L)
Prothrombin time			
Seconds over control	< 4	4–6	> 6
INR	< 1.7	1.7–2.3	> 2.3
Encephalopathy	None	Grade 1–2	Grade 3–4

Total score	Description	1-year survival	2-year survival
5–6	Class A: well-compensated disease	100%	85%
7–9	Class B: significant functional compromise	80%	60%
10–15	Class C: decompensated disease	45%	35%

Source: Child–Pugh classification of severity of liver disease;.[16] available from: www.uptodate.com

and the Child–Turcotte–Pugh calculator;[9] available from: www.hepatitisc.uw.edu/page/clinical-calculators/ctp

Information required

Acute HCV is diagnosed by medical history (which usually includes a recent risk event), abnormal liver function tests and the presence of HCV RNA to document viraemia. Antibodies to HCV appear approximately 6 weeks after exposure and, therefore, there is a window in which recently infected persons are HCV RNA-positive but do not have circulating antibodies; this may cause some diagnostic confusion.

The diagnosis of CHC is usually dependent upon the demonstration of circulating antibodies and HCV RNA for a period greater than 6 months. Criteria for PBS eligibility require evidence of chronic infection documented by repeated HCV antibody positivity and HCV RNA positivity.[5]

On initial evaluation the following investigations are performed on patients with CHC:

- FBC
- liver function tests
- coagulation profile
- plasma thyroid-stimulating hormone (TSH)
- HIV and HBV serology
- liver screen, including AFP
- HCV PCR
- HCV RNA with viral load is important for determining eligibility of 8-week course with sofosbuvir + ledipasvir
- HCV genotype is required by the PBS criteria, and significant before prescribing elbasvir + grazoprevir, or sofosbuvir + ledipasvir
- abdominal ultrasound.

Intense monitoring of patients on DAA therapy is usually not required. Depending on potential drug-drug interactions, assessment of adverse events and medication adherence, treatment and follow-up intervals should be optimised.

During treatment and post-treatment monitoring include LFTs and HCV PCR (qualitative) after 8-12 weeks. Hepatotoxicity should be monitored through LFTs at week 8 in patients treated with elbasvir plus grazoprevir.

No follow-up is required for patients with SVR, no cirrhosis and normal LFT results. For those LFT results are persistently abnormal, further evaluation for other liver diseases should be undertaken. Long term monitoring is required for patients with cirrhosis.

Transient elastography is increasingly used to evaluate liver fibrosis in HCV infection. HCC in patients with HCV usually occurs after cirrhosis is established. Hence, 6-monthly ultrasound and AFP measurements are undertaken in patients with cirrhosis for surveillance purposes.

Currently accepted treatments

All patients, except those with limited life expectancy due to non-liver or non-HCV-related comorbidities, should be considered for antiviral therapy given the current ease of access to therapy and high chance of successful sustained virological response.

To be eligible for PBS subsidy the patient must be at least 18 years old and must be:

- treated by a medical practitioner, or an authorised nurse practitioner experienced in the treatment of CHC infection, or

- in consultation with a gastroenterologist, hepatologist or infectious diseases physician experienced in the treatment of CHC infection.

Of recent, pan-genotypic antiviral therapy has opened up a path to antiviral management of all patients with HCV detected, irrespective of the genotyping. This may provide benefit in care situations where prompt delivery is likely to improve access to therapy, as genotype may take days to weeks to be obtained. Currently, following 3 highly efficacious, safe and well-tolerated pan-genotypic regimens are listed on the PBS for CHB:

- sofosbuvir + velpatasvir,
- glecaprevir + pibrentasvir, and
- sofosbuvir + velpatasvir + voxilaprevir.

Other DAA regimens are genotype-specific. See Table 6. The patient's history of antiviral therapy and fibrosis status are important factors in guiding the ongoing therapy. There is no restriction on access to treatment for patients with cirrhosis, however some toxicities must be considered in choosing a therapy for this patient group, and it is typically referred for specialist management. Patients with hepatocellular carcinoma should not be considered for antiviral therapy until six months after their tumour management has been completed.[5]

Liver transplantation is the treatment of choice for patients with end-stage liver disease. However, selected patients with decompensated cirrhosis (Childs Pugh B or C) may be considered for treatment with certain regimens in experienced or transplant centres. Regimens containing protease inhibitors are contraindicated in patients with decompensated cirrhosis.

Financial considerations

Table 7 summarises the commonly prescribed medications for HCV treatment and Table 8 summarises the commonly utilised MBS costs for treatment.

Prejudice to access and scarcity of resources

ESLD associated with HCV is the most frequent indication for liver transplantation. With reference to 'Sch4/4005-4007 – The Health Requirement' dated on July 2019 on the health-related criteria, liver transplantation has been identified to be short in supply. Refer also to section below on *Liver transplantation*.

Effect on applicant's ability to work

Adult patients with CHC usually carry on with their usual employment until the onset of decompensated liver disease. Some patients find it is impossible to continue with their usual employment whilst on antiviral therapy.

Table 6: *Chronic hepatitis C: Recommended protocols*

Recommended drug regimen	Genotype	Duration of treatment			
		Non-cirrhotic		Cirrhotic	
		Treatment naïve	Treatment experienced	Treatment naïve	Treatment experienced
Sofosbuvir and velpatasvir	Any genotype	12 weeks	12 weeks		
	Any genotype with decompensated cirrhosis. Use in combination with ribavirin. Genotype 3 with compensated cirrhosis. Consider addition of ribavirin.	-	-	12 weeks	12 weeks
Sofosbuvir, velpatasvir and voxilaprevir	Any genotype, who have failed a NS4A inhibitor	-	12 weeks	-	12 weeks
Glecaprevir and pibrentasvir	Genotype 1 who have failed regimens containing peginterferon, ribavirin, and/or sofosbuvir but no prior treatment experience with an HCV NS3/4A PI or NS5A inhibitor	-	8 weeks	-	-
	Genotype 1 who have failed regimens containing an NS3/4A PI	-	12 weeks	-	12 weeks
	Genotype 1 who have failed regimens containing an NS5A inhibitor	-	16 weeks	-	16 weeks
	Genotype 2, 4 and 6	8 weeks	8 weeks	12 weeks	12 weeks
	Genotype 3	8 weeks	16 weeks	12 weeks	16 weeks

Recommended drug regimen	Genotype	Duration of treatment			
		Non-cirrhotic		Cirrhotic	
		Treatment naïve	Treatment experienced	Treatment naïve	Treatment experienced
	Genotype 1 who have failed regimens containing peginterferon, ribavirin, and/or sofosbuvir but no prior treatment experience with an HCV NS3/4A PI or NS5A inhibitor	-	8 weeks	-	-
Daclatasvir and sofosbuvir	Genotype 1	12 weeks	12 or 24 weeks	24 weeks	24 weeks
	Genotype 3	12 weeks	12 weeks	24 weeks	24 weeks
Daclatasvir, sofosbuvir and ribavirin	Genotype 1	-	-	12 weeks	12 weeks
	Genotype 3	-	-	12 or 24 weeks	12 or 24 weeks
Grazoprevir and elbasvir	Genotype 1 or 4	12 weeks	12 weeks	12 weeks	12 weeks
Grazoprevir, elbasvir and ribavirin	Genotype 1a or 4 HCV who have experienced on-treatment virologic failure to prior treatment	-	16 weeks	-	16 weeks
Ledipasvir and sofosbuvir	Genotype 1 where pre-treatment HCV RNA < 6 million IU/mL	8 weeks	12 weeks	12 weeks	24 weeks
	Genotype 1 where pre-treatment HCV RNA > 6 million IU/mL	12 weeks			
Sofosbuvir and ribavirin	Genotype 2	12 weeks	12 weeks	12 weeks	12 weeks
	Genotype 3	24 weeks	24 weeks	24 weeks	24 weeks

Recommended drug regimen	Genotype	Duration of treatment			
		Non-cirrhotic		Cirrhotic	
		Treatment naïve	Treatment experienced	Treatment naïve	Treatment experienced
Sofosbuvir, peginterferon and ribavirin	Genotype 1, 3, 4, 5 & 6	12 weeks	12 weeks	12 weeks	12 weeks

PI: protease inhibitor.

Sources:

Hepatitis C guidelines.[10] Available from: www.hepcguidelines.org.au

Schedule of Pharmaceutical Benefits – effective 1–30 April 2019.[5] Available from: www.pbs.gov.au/info/publication/schedule/archive

Table 7: *Chronic hepatitis C: Cost of treatment protocols as of April 2019*

Drug regimens described in Table 6	PBS codes	PBS drug description	Unit cost*	Dose	Cost of treatment courses described in Table 6			
					8 weeks	12 weeks	16 weeks	24 weeks
Sofosbuvir and velpatasvir	11147Q	Sofosbuvir 400 mg + velpatasvir 100 mg tablet, 28	$12,651.04	Orally daily	-	$37,953	-	-
Sofosbuvir, velpatasvir and voxilaprevir	11658N	sofosbuvir 400 mg + velpatasvir 100 mg + voxilaprevir 100 mg tablet, 28	$12,651.04	orally daily	-	$37,953	-	$37,953

Drug regimens described in Table 6	PBS codes	PBS drug description	Unit cost*	Dose	Cost of treatment courses described in Table 6			
					8 weeks	12 weeks	16 weeks	24 weeks
Glecaprevir and pibrentasvir	11344C	Glecaprevir 100 mg + pibrentasvir 40 mg film-coated tablet, 84	$18,817.71	Orally 3 tablets daily	$37,635	$56,453	$75,271	-
Daclatasvir and sofosbuvir	10642D	Daclatasvir 60 mg tablet, 28	$7,817.71	Orally daily	-	$61,406	-	$122,812
	10624E	Sofosbuvir 400 mg tablet, 28	$12,651.04	Orally daily				
Daclatasvir, sofosbuvir and ribavirin	10642D	Daclatasvir 60 mg tablet, 28	$7,817.71	Orally daily	-	$62,701	-	-
	10624E	Sofosbuvir 400 mg tablet, 28	$12,651.04	Orally daily				
	10647J	Ribavirin 400 mg tablet, 28	$161.86	1,000 mg[a] orally daily				
Grazoprevir and elbasvir	11021C	Elbasvir 50 mg tablet + grazoprevir 100 mg, 28	$8,551.04	Orally daily	-	$25,653	-	-
Grazoprevir, elbasvir and ribavirin	11021C	Grazoprevir 100 mg + elbasvir 50 mg tablet, 28	$8,551.04	Orally daily	-	-	$35,823	-
	10673R	Ribavirin 400 mg tablet, 28	$161.86	1,000 mg[a] orally daily				
Ledipasvir and sofosbuvir	10628J	Ledipasvir 90 mg + sofosbuvir 400 mg tablet, 28	$12,651.04	Orally daily	$25,302	$37,953	-	$75,906
Sofosbuvir and ribavirin	10624E	Sofosbuvir 400 mg tablet, 28	$12,651.04	Orally daily	-	$39,248	-	$78,334
	10647J	Ribavirin 400 mg tablet, 28	$161.86	1,000 mg[a] orally daily				

Drug regimens described in Table 6	PBS codes	PBS drug description	Unit cost*	Dose	Cost of treatment courses described in Table 6			
					8 weeks	12 weeks	16 weeks	24 weeks
Sofosbuvir and velpatasvir	11147Q	Sofosbuvir 400 mg + velpatasvir 100 mg tablet, 28	$12,651.04	Orally daily	-	$37,953	-	-
Sofosbuvir, peginterferon and ribavirin	10624E	Sofosbuvir 400 mg tablet, 28	$12,651.04	Orally daily	-	$43,065	-	-
	11037X	PEG-IFN-alfa-2a 180 microgram/0.5 mL injection 4 x 0.5 mL syringes	$1,272.27	180 microgram PEG-IFN SC once a week				
	10647J	Ribavirin 400 mg tablet, 28	$161.86	1,000 mg[a] orally daily				
Sofosbuvir, velpatasvir and voxilaprevir	11658N	sofosbuvir 400 mg + velpatasvir 100 mg + voxilaprevir 100 mg tablet, 28	12,651.04	orally daily	-	$37,953	-	-

[a] Ribavirin dose is 1,000 mg for individuals weighing < 75 kg, and 1,200 mg for those weighing ≥ 75 kg. A dose of 1,000 mg has been assumed for deriving cost estimates.

*Unit cost of drug = Dispensed Price for Maximum Quantity (DPMQ)/Max qty packs.

Source: Schedule of Pharmaceutical Benefits – effective 1–30 April 2019.[5] Available from: www.pbs.gov.au/info/publication/schedule/archive

Table 8: Chronic hepatitis C: MBS and other medical service costs as of April 2019

Service	MBS item	Frequency	Unit cost
Medical			
GP consultation	23	2 per year	$37.60
Specialist consultation – Treatment and management plan	132	Once per year	$267.85
Specialist consultation – Subsequent consults for patient with 2 or more comorbidities	133	8 per year (if on therapy)	$134.10
Specialist consultations – Subsequent consults for patient with no comorbidities	116	8 per year (if on therapy)	$76.65
Diagnostics			
Test for HCV (or HBV) antigen/antibodies to determine immune status or viral carriage	69475	Initial diagnosis	$15.65
HCV detection	69445	Initial assessment	$92.20
Quantitation of HCV RNA load in plasma or serum in the pre-treatment evaluation	69488	Testing for HCV viral load at initial diagnosis, and 4 per year if on therapy	$180.25
Quantitation of HCV RNA load in the pre-treatment evaluation by specialist	69478	6-month intervals	$29.25
HCV genotype	69491	Initial assessment	$204.80
FBC Liver function test Electrolytes and BGL (costs calculated for stable disease)	66512	Initial assessment, and monthly for 1 year on therapy or every 6 months in stable disease	$17.70
Coagulation profile	65120	Initial assessment	$13.70
Plasma TSH	66719	Initial assessment, and monthly for 1 year on therapy	$34.80
AFP; the detection or monitoring of hepatic tumours	66650	Initial assessment, and every 6 months if cirrhosis	$24.35
Abdominal ultrasound	55036	Initial assessment, and every 6 months if cirrhosis	$111.30

BGL: blood glucose level.

Service	MBS item	Frequency	Unit cost
Source of unit cost data: Medicare Benefits Schedule operating from 01 April 2019.[4] Available from: www.health.gov.au/internet/mbsonline/publishing.nsf/Content/downloads Unit values are presented up to 2 decimal places. Total costs have been computed on these unit values, and rounded to the nearest whole number.			

Table 9: *Chronic hepatitis B/C: Hospital costs as of April 2019*

Code	Description	Average cost*
Inpatient admissions†		
H63A	Other disorders of liver, Major complexity	$13,725
H63B	Other disorders of liver, Intermediate complexity	$4,534
H63C	Other disorders of liver, Minor complexity	$2,379
Outpatient services‡		
20.25	Gastroenterologist consultation, management, treatment and education on all types of diseases of the stomach and intestine, including hepatitis	$832
20.44	Infectious diseases specialist consultation (includes treatment of HBV and HCV)	$977
*Only hospital costs included; does not include cost of drugs. †Diagnostic Related Groups (DRGs) identified based on accompanying Definitions Manual. AR-DRG code Version 9.0.[11] ‡Service events identified based on Tier 2 non-admitted definitions manual 2016–17 version 4.1.[13]		
National Hospital Cost Data Collection Round 21.[12] Available from: www.ihpa.gov.au/publications/national-hospital-cost-data-collection-report-public-sector-round-21-financial-year		

Hepatitis D

Definition and brief description of hepatitis D

HDV requires the presence of HBV to replicate; hence, hepatitis D is found only in patients with HBV. HDV is relatively uncommon in Australia.

As with HBV, hepatitis D is transmitted through blood or body fluids of an infected person.

Infection with HDV can either be simultaneous with HBV; that is at the time of HBV acquisition (referred to as co-infection), or as in a person already infected with HBV (known as superinfection).

Only confirmed HDV cases should be notified to the Commonwealth's NNDSS.[6]

Prognosis, factors affecting progression, including rate of progression

Acute liver failure is about 10 times more common after acute infection with HDV than in other types of viral hepatitis.

Co-infections of HBV and HDV are usually acute, self-limited infections. The infection becomes chronic in less than 5% of HBV-HDV co-infected patients.

Superinfection with HDV in a chronically infected HBV patient leads to chronic hepatitis D in approximately 80% of cases. HDV superinfection tends to enhance the frequency and severity of clinical sequelae of chronic HBV infection.

Approximately 60–70% of patients with chronic hepatitis D develop cirrhosis within 5–10 years.

HCC occurs in chronically infected HDV patients with advanced liver disease with the same frequency as in patients with HBV.

Information required

Chronic HDV infection is detected by serological tests (acute infection: IgM anti-HDV; chronic infection: IgM anti-HDV, IgG anti-HDV), and by the presence of hepatitis D RNA.

Currently accepted treatments

PEG-IFN has recently been shown to be an acceptable therapy for chronic HDV, but high doses are required and sustained virologic response rates (SVR) vary between 20–43%. Many patients are unsuitable for therapy because of advanced liver disease.

Hepatitis E

Definition and brief description of hepatitis E

Hepatitis E virus (HEV) is transmitted by the faecal-oral route, usually through contaminated water. Recent evidence suggests that hepatitis E can be acquired by consumption of meat of animals in the wild.

HEV is more common in developing countries, and only occasional cases have been reported in Australia (most often following travel to other countries).

Only confirmed hepatitis E cases should be notified to the Commonwealth's NNDSS.[6]

Prognosis, factors affecting progression, including rate of progression

Acute hepatitis E does not progress to chronic infection unless in the setting of immunosuppression.

The disease is usually mild, but occasionally the acute infection will progress to a fulminant form. This is more common in pregnant women, whereby the case fatality rate approaches 20%. The overall case fatality rate is less than 1%.

Information required

The presence of anti-HBE antibody (IgM) in the serum confirms the disease and persists for at least 6 weeks. IgG antibody peaks shortly after and remains detectable for some years.

Laboratory diagnosis also includes PCR testing.

Currently accepted treatments

There is no specific antiviral therapy for hepatitis E.

Ribavirin has been used successfully in the treatment of HEV in some cases.

Liver transplantation

Selection of patients for liver transplantation

Source: Consensus statement.[15] Available from: https://donatelife.gov.au/resources/clinical-guidelines-and-protocols/clinical-and-ethical-guidelines-organ-transplantation

A candidate for liver transplantation must have irreversible acute or chronic ESLD refractory to other forms of conventional medical or surgical therapy. The number of people undergoing liver transplantation is limited by donor availability. Mortality for people on the liver transplant waiting list is around 10–15%.

Inclusion criteria[15]

Patient should have at least one of the conditions listed below.

- Chronic liver disease with life-threatening complications. The principle indication in patients with ESLD is:
  - for adults: Model for End-Stage Liver Disease (MELD)[a] score > 15
  - for children: Paediatric End-Stage Liver Disease (PELD)[b] score > 17.
- Small HCCs that fulfil the University of California San Francisco (UCSF) criteria.[c]
- Other indications include:
  - liver disease that would result in a 2-year mortality rate > 50% without liver transplantation
  - diuretic-resistant ascites
  - recurrent hepatic encephalopathy, recurrent spontaneous bacterial peritonitis
  - recurrent or persistent gastrointestinal haemorrhage
  - intractable cholangitis (in primary or secondary sclerosing cholangitis patients)
  - hepatopulmonary syndrome
  - portopulmonary hypertension

[a] MELD score = 0.957 x loge (creatinine [mg/dL]) + 0.378 x loge (bilirubin [mg/dL]) + 1.120 x loge (INR) + 0.643.

Multiply the score by 10 and round to the nearest whole number. Laboratory values < 1.0 are set to 1.0 for the purposes of the MELD calculation. The maximum serum creatinine is 4.0 mg/dL. This includes those patients on dialysis.

[b] PELD score = 0.480 x loge (bilirubin [mg/dL]) + 1.857 x loge (INR) – 0.687 x loge (albumin [g/dL]) +

0.436 if patient is < 1 year old + 0.667 if the patient has growth failure (< -2 standard deviations).

Multiply the score by 10 and round to the nearest whole number. Laboratory values < 1.0 are set to 1.0 for the purposes of the PELD calculation.

[c] HCC MELD: If the maximum tumour diameter is ≤ 2 cm there will be no HCC MELD points allocated to the patient. That patient's score will be the standard MELD score only. If the maximum tumour diameter is > 2 cm but total tumour burden is within UCSF criteria (no tumour > 6.5 cm in diameter and total diameter of all tumours not more than 8 cm), then a score of 22 will be allocated to the patient. An additional 2 points will be allocated for every 3 months on the transplant waiting list.

- metabolic syndromes (with severe or life-threatening symptoms) that are curable with liver transplantation (e.g. familial amyloidosis, urea cycle disorders, oxalosis)
- polycystic liver disease with severe or life-threatening symptoms
- hepatoblastoma in children
- intractable itch secondary to cholestatic liver disease.

Combined liver–kidney transplantation would only be offered to those liver disease patients with one of the following:

- known chronic kidney disease requiring dialysis
- chronic kidney disease not requiring dialysis but with an estimated glomerular filtration rate (GFR) < 30 mL/min and proteinuria > 3 g/day, or with a GFR < 20 mL/min for >3 months
- acute kidney injury (including hepatorenal syndrome) not requiring dialysis but with an estimated GFR

< 25 mL/min for > 6 weeks

- known metabolic disease including hyperoxaluria, atypical haemolytic uraemic syndrome with factor H deficiency, or familial amyloidosis affecting primarily the kidney.

Patients will be considered for re-transplantation if they fulfil the above criteria for either acute or chronic liver disease, with an expected post-transplant survival rate exceeding 50% at 5 years.

Exclusion criteria[15]

Patients with conditions or circumstances that would make a post-transplant survival rate of >50% at 5 years unlikely are excluded. Examples of exclusion include:

- malignancy (prior or current condition, except for HCC within UCSF criteria)
- active infection (other than HBV, HCV or HIV)
- coronary artery disease that is irremediable or associated with a poor prognosis
- cerebrovascular disease that is irremediable or associated with a poor prognosis
- severe metabolic syndrome (hypertension, morbid obesity, hyperlipidaemia and type II diabetes, with or without obstructive sleep apnoea)
- patients with alcoholic liver disease who experience social instability, alcohol problems in first-degree relatives, who are < 50 years old, have had repeated alcohol cessation treatment failures, find it difficult to comply with medical care, currently are polydrug abusers and/or who have a co-existing severe mental disorder — such patients are very unlikely to remain abstinent in the post-transplant period
- tobacco use is a relative contraindication to liver transplantation (because of an increased risk of malignancy and cardiovascular disease)
- inadequate or absent social support is a relative contraindication to liver transplantation (because of an increased risk of non-adherence)
- severe neurocognitive impairment and/or developmental delay in a potential paediatric candidate.

Allocation of a donor liver[15]

Allocation of a donor liver is based on medical need, medical urgency, capacity to benefit, donor/recipient matching and logistical factors. Prioritisation of donor liver allocation is as listed below.

1. Patients listed as 'urgent'. These are further categorised into the following 4 categories:
    a. Status 1: patients suitable for transplantation with acute liver failure who are ventilated and in an intensive care unit (ICU) as at risk of imminent death. When such patients are listed, allocation to them is mandatory.
    b. Status 2a: patients suitable for transplantation with acute liver failure from whatever cause who are not yet ventilated but meet the King's College Hospital criteria.[d] This includes patients who have acute liver failure because of vascular thrombosis in a liver allograft.

       In addition, this category includes paediatric candidates with severe acute or chronic liver disease who have deteriorated and are in a paediatric ICU. When such patients are listed, allocation to them is usual but not mandatory and subject to discussion between the directors (or delegates) of the donor and recipient state (or New Zealand) liver transplant centres.
    c. Status 2b: paediatric patients suitable for transplantation who suffer from severe metabolic disorders or hepatoblastoma (after initial treatment), for whom a limited window exists during which liver transplant is possible.
    d. Status 2c: patients awaiting combined liver–intestine transplant by the National Intestinal Transplantation Program in Victoria. If a potentially suitable donor is identified, the home unit must discuss allocation of donor organs with the Victoria unit unless the home unit has a suitable liver recipient with a MELD score ≥ 25.
2. If no patient is listed in the urgent category, then the local liver unit will allocate livers according to the following principles:
    a. the liver will go to the ABO-identical blood group recipient with the highest MELD or PELD score;
    b. the following factors also will be considered (and the reason for the variant allocation noted):
        i. the presence of a patient on the list with HCC whose HCC MELD score exceeds the standard MELD score of other patients on the list of the same ABO blood group
        ii. the quality of the donor liver — poor quality donor livers may be utilised, but may require transplantation into recipients with lower MELD scores to ensure success
        iii. the presence of a paediatric patient on the waiting list in need of a split or reduced-size liver, provided the donor liver is of suitable quality
        iv. if the donor is paediatric, then paediatric recipients will have priority for that liver for size reasons
        v. donor size — overly large size discrepancies result in poor outcomes; size matching may result in patients without the highest MELD or PELD scores being allocated a liver

[d] King's College Hospital criteria for liver transplantation in acute liver failure:

- paracetamol (acetaminophen)-induced liver failure: pH of arterial blood (after rehydration) < 7.3, or all 3 of the following: INR > 6.5; serum creatinine > 300 micromol/L; and Grade III or IV encephalopathy

- non-paracetamol-induced acute liver failure: INR > 6.5, or 3 of the following 5 criteria: age < 11 or > 40 years; serum bilirubin > 300 micromol/L; jaundice-to-coma time > 7 days; INR > 3.5; and drug toxicity.

vi. logistical concerns — transport, cold storage preservation time, surgeon and operating room staff skill mix and availability, along with the anticipated hepatectomy time may impact on allocation and result in patients without the highest MELD or PELD scores being allocated a liver

vii. the presence of a patient on the waiting list who has a condition that will not result in a MELD, PELD or HCC MELD score that allows prioritisation — such patients will usually have severe, correctable extrahepatic disease that mandates some priority of allocation (e.g. familial amyloidosis, oxalosis, protein C deficiency) that is nevertheless a variance.

3. Whenever possible, paediatric donor liver is allocated to paediatric recipients.

Prognosis after liver transplantation

Table 10: *Survival rate post-liver transplant*

Patient	1 year	5 years	10 years	20 years
Adult	90%	83%	75%	56%
Child	90%	86%	83%	79%
Source: Australia and New Zealand Liver Transplant Registry 29th report.[3] Available from: https://www3.anzltr.org/				

Survival is better in chronic than acute liver failure. Children have a significantly better survival rate than adults. Current Australian liver transplant survival rates are given in Table 10.

Treatment of HCV on the waiting list or following transplant is now routine management for patients with advanced disease on the transplant program. The SVR to antiviral therapy is not different to other patients; combinations of three antiviral therapy for patients who have previously failed antiviral therapy and are suspected to have resistant strains of the virus show promise in eradicating this infection in all patients.

In the past, CHB had the poorest outcome among patients with non-malignant disorders undergoing liver transplant due to disease recurrence. In Australia, transplant recipients with CHB may receive long-term monthly intramuscular low-dose hepatitis B immunoglobulin (HBIG) in combination with oral DAAs such as entecavir or tenofovir. This regimen has been associated with low rates (< 2%) recurrence of HBV within 5 years after transplantation. This protocol is relatively inexpensive and well tolerated by patients. The protocol used in Australia differs significantly from expensive and inconvenient protocols used in most other countries, where high-dose intravenous HBIG and oral DAA is the standard of care.

Post-transplant recurrence of primary biliary cirrhosis, autoimmune hepatitis and primary sclerosing cholangitis has been reported, but appears to be very rare.

Management of liver transplants

Transplant assessment

Before transplantation, the patient undergoes a number of tests and procedures to assess suitability.

Assessment and management differ according to whether the patient has acute liver failure, chronic liver failure or another indication.

In patients with acute liver failure, assessment and management will include:

- determination of aetiology of liver failure via history, blood testing, imaging and occasionally transjugular liver biopsy

- admission and management in an ICU, transfer to transplant facility and placement on transplant list, if appropriate (decision based on medical and psychosocial factors)
- monitoring of intracranial pressure and evaluation for signs of intracranial hypertension, as indicated (according to centre practice)
- arterial and central venous pressure monitoring and management
- endotracheal intubation and ventilation, renal support therapy if indicated (usually haemofiltration), systemic inotrope support as indicated
- specific management of the cause of liver failure (e.g. N-acetylcysteine infusion, antiviral drugs, corticosteroids, etc)
- prophylactic antibacterial and antifungal medications
- support of coagulopathy (vitamin K, blood products)
- prophylaxis against gastrointestinal haemorrhage (proton pump inhibitors or H2-receptor antagonists)
- nutritional support (enteric feeding).

In acute liver failure, initial laboratory analysis may involve:

- prothrombin time/INR
- chemistry:
  - sodium, potassium, chloride, bicarbonate, calcium, magnesium, phosphate
  - glucose
  - aspartate aminotransferase (AST), ALT, alkaline phosphatase, gamma-glutamyl transpeptidase (GGT), total bilirubin, albumin
  - creatinine, blood urea nitrogen.
- arterial blood gas
- arterial lactate
- FBC
- blood type and screen
- toxicology screen, including paracetamol level (if indicated)
- viral hepatitis serologies if indicated, or to establish underlying infection (including HAV, HBV, HCV, HEV, Epstein–Barr virus [EBV] and cytomegalovirus [CMV])
- ceruloplasmin level if indicated (Wilson disease consideration)
- arterial ammonia level
- autoimmune markers
- antinuclear antibody (ANA), anti-smooth muscle antibody (ASMA) and Ig levels
- HIV status
- amylase and lipase.

Procedures may include:

- abdominal ultrasound
- abdominal and cerebral CT scan (if stable enough and normal renal function)
- echocardiography.

Patients with chronic liver failure undergo transplant assessment either in an ambulatory setting (if possible), or as an inpatient if necessary. Standard assessment may include:

- blood tests
- FBC, activated partial thromboplastin time (APTT), INR
- biochemistry (electrolytes [sodium, potassium, chloride], urea and creatinine; liver function test; amylase; lipase)
- blood group
- viral serology (HAV, HBV, HCV, CMV, EBV, varicella zoster virus, herpes simplex virus, adenovirus)
- autoimmune serology:
  - prospective recipients and donors will undergo immunological screening/matching to determine suitability of a particular recipient to receive a particular donor organ; this will likely include ABO blood group matching, matching of minor red blood cell antigens, lymphocyte cross-match and evaluation for presence of donor-specific antibodies (which may be a relative contraindication to transplant or result in immunosuppressive therapy to reduce the risk of acute rejection).
- endocrine assessment (thyroid function tests, testosterone)
- bone assessment (25-hydroxyvitamin D [25-OH vitamin D], parathyroid hormone [PTH], Ostase assay, bone mineral density scan [DEXA])
- radiologic assessment (chest x-ray, cerebral CT scan, abdominal CT scan)
- patients with HCC will be staged with abdominal, chest and cerebral CT, as well as bone scan. In most patients, magnetic resonance imaging (MRI) or angiogram-CT scan will be performed
- cardiorespiratory assessment (lung function tests, arterial blood gases, echocardiogram, dobutamine stress echocardiogram, coronary angiogram (if indicated)
- endoscopy (to assess for oesophagogastric varices); colonoscopy (if iron deficiency, history of primary sclerosing cholangitis or inflammatory bowel disease).

Post-transplant management

Immunosuppression

All liver transplant recipients require lifelong immunosuppression to prevent allograft rejection.

The majority of patients are started on a double-therapy regimen of corticosteroids and a calcineurin inhibitor, such as ciclosporin or tacrolimus, or a triple-therapy regimen, including azathioprine 1 mg/kg/day or mycophenolate mofetil 1 g twice daily (not available on PBS for this indication). Immunosuppressive therapy is commenced within 24 hours of transplantation (usually an intraoperative dose of methylprednisolone 1 g is given). In patients with significant renal impairment, a renal-sparing protocol with basiliximab (2 doses on day 1 and day 5) and a low-dose calcineurin inhibitor may be used.[7]

Tacrolimus and ciclosporin doses are adjusted according to therapeutic drug monitoring. Target levels vary according to time post-transplantation and underlying aetiology of the liver disease. In long-term follow-up patients, only very low doses are required.

Prednisone is tapered according to centre-specific protocols. Most patients are on 5 mg daily by 3 months post-transplantation.

The optimal immunosuppression protocol for patients transplanted for CHC has not been defined, although most centres will institute steroid withdrawal at some time between 3 and 12 months post-transplantation.

Antimicrobial prophylaxis

Intravenous antibiotics are usually administered for 72 hours. CMV prophylaxis with valganciclovir 900 mg daily is given to patients at risk of CMV reactivation (recipient CMV Ab positive), or at risk of *de novo* infection (donor CMV Ab positive, recipient negative). Duration is for 3–6 months. *Pneumocystis carinii* prophylaxis with low-dose cotrimoxazole (e.g. 3 tablets per week) is given for 12 months. Antifungal prophylaxis with low-dose fluconazole is used in selected patients.

Patients with CHB receive prophylaxis with lamivudine (or another oral antiviral agent) and low-dose intramuscular HBIG. Patients receive daily HBIG injections for 1 week, followed by weekly injections for a further 3 weeks and then lifelong monthly injections. Lamivudine 100 mg daily (or other oral agents, such as entecavir 0.5 mg daily) is usually commenced while on the waiting list (if not before) and continued lifelong.

Acute rejection

Acute rejection occurs in fewer than half of patients, but this is easily treated in most cases with extra steroids or by altering the drug regimen. Severe rejection is very uncommon. Occasionally, pulse methylprednisolone therapy is required, but more intensive therapy with muromonab-CD3 (OKT3) is rarely required. In patients with recurrent HCV, treatment with pulse steroids or OKT3 is avoided as such treatments lead to worsened outcomes.

Management of diabetes

Diabetes mellitus occurs in approximately 30% of liver transplant recipients. The incidence is highest in patients transplanted for hepatitis C, and in those with pre-existing diabetes. The incidence of diabetes relates to the specific immunosuppressive protocol used.

Management requires blood glucose monitoring, adjustment of immunosuppression, oral hypoglycaemic agents or insulin, as required. Consultation with a Diabetes Centre or endocrinologist is frequently required.

Management of hypertension

Hypertension is related to the immunosuppressive protocol in most patients. Frequently, adjustment of the immunosuppressive therapy is sufficient management. Some patients require long-term therapy with beta-blockers, angiotensin-converting enzyme (ACE) inhibitors or calcium antagonists.

Management of hyperlipidaemia

Hyperlipidaemia is related to the immunosuppressive protocol in most patients. Therapy is according to established guidelines for the broader community.

Management of metabolic bone disease

Osteoporosis and osteopenia are common in patients with chronic liver disease. Bone loss worsens in the first 3 months post-transplant because of factors related to immobility, surgery and high-dose corticosteroids. All patients should receive supplementation with vitamin D and calcium.

Intravenous bisphosphonate therapy can prevent bone loss in the early post-transplant period and is particularly indicated in patients with underlying osteopenia or osteoporosis.[7]

Post-transplant monitoring

Patients are discharged when clinically stable and able to cope outside of hospital. Most patients are discharged at 2–3 weeks post-transplant, although longer admissions are required in patients who develop complications.

Patients are monitored in an ambulatory setting. In general, they are seen weekly for the first 6 weeks post-transplant, second-weekly up to 12 weeks, monthly up to 12 months and then 3-monthly thereafter.

Monitoring comprises clinical assessment for complications and adverse drug reactions, as well as blood tests for therapeutic drug monitoring, assessment of liver and renal function, FBCs, lipids, glucose and glycosylated haemoglobin and recurrent disease (HCV RNA quantitative testing, HBsAg and anti-HBs, AFP, as indicated).

Doppler ultrasound of the allograft may be performed at 2–3 months post-transplant (according to local practice). Transient elastography (FibroScan® may also be used in the hepatitis C setting to detect rapidly progressive fibrosis) in lieu of liver biopsy may be performed, though this would be dependent upon the treating centre and local expertise/opinion; of note, this is not covered through the Medicare subsidy.

Treatment of CHC before or after transplant

Treatment of CHC post-transplant is safe and effective using any of the four standard regimens listed above, following standard protocols for use of these agents in non-cirrhotic patients. There have been several trials of the transplantation of organs from HCV positive non-viremic donors into HCV negative recipients, with no evidence of infection post-transplant. There is good evidence to suggest that this is a safe and effective strategy for organ donation.[17]

Financial considerations

Table 11 shows the average inpatient cost of a liver transplant at almost $170,000 per recipient (DRG H09Z). Where rejection or failure occurs, patients are assigned to DRG codes H63A and H63B.

Table 12 lists common pharmaceutical regimens given to patients following discharge over the months post-transplantation. Specialist costs are given in Table 13.

Table 11: *Liver transplant: Hospital costs as of April 2019*

Code	Description	Average cost*
Inpatient admissions†		
H09Z	Liver transplant	$166,134
H63A	Other disorders of liver, Major complexity	$13,725
H63B	Other disorders of liver, Intermediate complexity	$4,534
H63C	Other disorders of liver, Minor complexity	$2,379
Outpatient services‡		
20.01	Transplants	$553
*Only hospital costs included; does not include cost of drugs.		

Code	Description	Average cost*
†DRGs identified based on accompanying Definitions Manual. AR-DRG code Version 9.0.[11] ‡Service events identified based on Tier 2 non-admitted definitions manual 2016–17 version 4.1.[13]		
National Hospital Cost Data Collection Round 21.[12] Available from: www.ihpa.gov.au/publications/national-hospital-cost-data-collection-report-public-sector-round-21-financial-year		

Table 12: Liver transplant: Costs of commonly prescribed medications as of April 2019

Drug	PBS code	Usual dose/ frequency	Unit cost	Estimated annual cost	
Antimicrobial prophylaxis					
Trimethoprim 160 mg + sulfamethoxazole 800 mg tablet, 10	2951H	1 tablet 3 times per week for 12 months	$13.22	$212	
Valganciclovir 450 mg tablet, 60	6357N	900 mg daily for 3–6 months (prevention of CMV infection)	$1,064.53	$6,387	
Fluconazole 200 mg capsule, 28	1475P	200 mg daily for 30 days (in selected patients)	$51.70	$103	
Azathioprine					
Azathioprine 25 mg tablet, 100	2688L	1 mg/kg/day as single daily dose (assume adult weight 70 kg for costing)	$23.49	$258	
Mycophenolate					
Mycophenolate mofetil 500 mg tablet, 50	8650G	Twice per day 12 hours apart	$51.05	$766	
Ciclosporin					
Ciclosporin 25 mg capsule, 30	8658Q	Target C2 level 1,200 after 3 months post-transplant; usually stabilising at 100–200 mg daily, 2 doses 12 hours apart (assume 1 dose every 12 hours for costing)	$40.31	$1,008	Average = $2,272
Ciclosporin 50 mg capsule, 30	8659R		$77.75	$1,944	
Ciclosporin 100 mg capsule, 30	8660T		$154.53	$3,863	

Drug	PBS code	Usual dose/ frequency	Unit cost	Estimated annual cost	
Tacrolimus					
Tacrolimus 500 microgram capsule, 100	8646C	Initially, target trough level 12–15 up to 3 months post-transplant; gradually 8–10 within a year; target level reducing to 5–8 beyond 1 year (assume 1 dose every 12 hours for costing)	$129.28	$1,034	Average = $4,085
Tacrolimus 1 mg capsule, 100	8647D		$249.19	$1,994	
Tacrolimus 5 mg capsule, 50	8648E		$615.11	$9,227	
Intravenous methylprednisolone and/or oral prednisone					
Methylprednisolone 40 mg injection [5 x 40 mg vials] (&) inert substance diluent [5 x 1 mL vials], 1 pack	2981X	200 mg first day; reducing to 20 mg daily from days 7–30; 15 mg daily to day 60; 10 mg daily to day 90; then 5 mg single daily dose	$40.96	$169	
Prednisolone 5 mg tablet, 60	1935W		$14.24		
Source: Schedule of Pharmaceutical Benefits – effective 1–30 April 2019.[5] Available from: www.pbs.gov.au/info/publication/schedule/archive Unit cost of drug = Dispensed Price for Maximum Quantity (DPMQ)/Max qty packs. Unit values are presented up to 2 decimal places. Total costs have been computed on these unit values, and rounded to the nearest whole number of full pack size costs.					

Table 13: *Liver transplant: MBS and other medical service costs (once discharged from hospital) as of April 2019*

Service	MBS item	Frequency	Unit cost	Estimated annual cost
Medical				
GP consultation	23	9 annually	$37.60	$338
Specialist consultations	116	Weekly to week 6, second-weekly to week 12, monthly to 12 months, then 3-monthly thereafter	$76.65	$920
Diagnostic				
Biochemistry	66512	Weekly to week 6, second-weekly to week 12, monthly to 12 months, then 3-monthly thereafter	$17.70	$637

Service	MBS item	Frequency	Unit cost	Estimated annual cost
Prothrombin time/ INR		Monthly		
FBC		Weekly to week 6, second-weekly to week 12, monthly to 12 months, then 3-monthly thereafter		
CMV viral load	69384	Annually	$15.65	$16
Procedural				
Ultrasound	55036	1 at 2–4 weeks post-transplant, then as indicated	$111.30	$223
CT scan	61361	As indicated	$461.40	$461
MRI	63482	As indicated	$403.20	$403
Colonoscopy	32090	Annual in patients with primary sclerosing cholangitis, ulcerative colitis	$334.35	$334
Liver biopsy	30409	As indicated	$174.45	$174
Bone density scanning	12306	1–2 yearly as indicated	$102.40	$102

Source: Medicare Benefits Schedule operating from 01 April 2019.[4] Available from: www.health.gov.au/internet/mbsonline/publishing.nsf/Content/downloads

Unit values are presented up to 2 decimal places. Total costs have been computed on these unit values, and rounded to the nearest whole number.

Prejudice to access and scarcity of resources

With reference to 'Sch4/4005-4007 – The Health Requirement' dated July 2019 on the health-related criteria, liver transplantation has been identified to be short in supply. It is limited by severe donor organ shortage. Liver transplantation in Australia is limited to Australian citizens and permanent residents in Australia.

In view of the existing gap between donor organ need and availability, assessment of international patients (non-Australian citizens or permanent residents) is not considered for possible transplantation, except under exceptional circumstances. An example of this might be when an international visitor develops acute organ failure that would normally warrant consideration for transplantation but is too unwell to return to their home country. In this situation, it needs to be established that the visitor will return to an environment that permits appropriate ongoing post-transplant surveillance and treatment.[15]

Consequently, if an applicant is deemed to require kidney transplantation, then this will cause significant prejudice to access, resulting in existing Australian residents having to wait longer for this limited service. As of 31 December 2017, there were 167 patients on the waiting list. Median waiting time to transplant was 128 days.[3]

Effect on applicant's ability to work

Patients with multiple postoperative complications may spend many months in hospital, including periods in ICU, and may need repeat surgery, multiple imaging procedures, multiple blood tests and multiple interdisciplinary consultations. Patients with an uncomplicated transplant require brief hospitalisation and return to good health in 3–6 months. After successful transplantation patients have a greatly improved lifestyle and are often able to return to school or work and normal social activities.

Appendix: Clinical scenarios

Scenario 1: HCV antibody-positive, HCV PCR-negative

A 53-year-old male healthcare worker was found to have the HCV antibody when tested before entry through an Australian visa. The applicant was born in South Asia and had received a blood transfusion after a motor vehicle accident in 1979. He doesn't have any other medical conditions and is with normal live enzymes. On further testing, the HCV PCR test is negative.

Clinical opinion

This individual was probably infected after the blood transfusion (although it is possible that mass vaccination programs have contributed to the high prevalence of HCV in some countries), or possibly due to needle stick injury/exposure at the workplace. He has cleared the HCV virus; accordingly, he will not require any additional medical investigation, treatment or follow-up.

Scenario 2: Chronic hepatitis B

A 39-year-old woman is found to be HBsAg-positive and HBc-Ab positive on screening. She is assumed to have acquired HBV in childhood. Her liver enzyme levels are within the normal range and her HBV viral load is low. She does not drink alcohol. She is well and has no signs of liver disease.

Clinical opinion

From these tests, she appears to have no signs of significant liver injury and is in the immune control phase. In the following 12 months she will require testing for hepatitis serology, HBV viral load and liver enzymes every 6 months. She is at low risk of developing advanced liver disease and its related complications. Antiviral drugs are not likely to be required at this stage of her infection. About 10–20% of subjects in the immune control phase progress to the immune escape of the infection through 4th or 5th decade of life. She would then benefit from the commencement of anti-viral therapy.

Table 14: *Scenario 2: Chronic HBV: Annual costs as of April 2019*

Service	MBS item	Frequency	Unit cost	Estimated annual cost
Medical				
GP consultation	23	2 per year	$37.60	$75
Specialist consultation – Treatment and management plan	132	1 per year	$267.85	$268
Specialist consultations	116	1 per year	$76.65	$77
Subtotal				$420
Diagnostics				
HBV serology (complete)	69484	Every 12 months	$17.10	$17
HBV DNA	69482	Every 12 months on therapy	$152.10	$152
FBC including liver enzymes	66512	2 per year	$17.70	$35
ALT	66509	2 per year	$15.65	$31
Subtotal				$235
Total				**$655**

Unit values are presented up to 2 decimal places. Total costs have been computed on these unit values, and rounded to the nearest whole number.

Scenario 3: Chronic HBV (with/without HBeAg) with abnormal ALT and VL

The applicant is a 50-year-old man who was infected as a result of an unhygienic surgical procedure 7 years previously. He presents with lethargy. He is HBsAg-positive, anti-HBc-positive and HBeAg-positive with ALT of 150 U/L. His liver elastography is 8.7 kPa, IQR 0.7; this is an indeterminant result that raises concerns regarding moderate liver fibrosis. He has a high HBV viral load of 100,000 IU/mL. His hepatitis D serology is negative. He drinks alcohol regularly. His clotting studies are mildly elevated.

Clinical opinion (with HBeAg)

The annual incidence of cirrhosis is 2–6%. In view of the risk of cirrhosis, as well as HCC, he will benefit from oral antiviral therapy, though interferon therapy may be considered too.

The applicant will require careful ongoing monitoring. Unfortunately, many patients with HBeAg do not seroconvert; thus, he is likely to require lifelong treatment.

Clinical opinion (without HBeAg)

Consider another patient similar to the above applicant, but without HBeAg. Although patients with HBeAg-negative disease tend to have lower HBV viral load than those with HBeAg-positive infection (< 20,000 IU/mL vs > 20,000 IU/mL), they often display increased hepatic injury on liver biopsy. Consequently, the annual incidence of cirrhosis is significantly higher (8–10%) in HBeAg-negative chronic HBV patients, compared to that in HBeAg-positive patients (2–6%).

Although the duration of nucleoside analogue therapy in a patient with immune escape (HBeAg-negative at the start of treatment) has not been established, it is usually required for more than 1 year and likely to be continued for > 8 years. The aim of long-term treatment is to prevent or delay the onset of complications including cirrhosis, hepatic decompensation and HCC. It is recommended that the threshold serum HBV DNA level for initiating antiviral therapy should be 2,000 IU/mL in this group of patients.

Unlike PEG-IFN, oral nucleos(t)ide analogues do not induce a strong immune response and, thus, are likely to require long-term administration to prevent relapse.

NOTE: Unlike the previous applicant with HBeAG, this patient faces an annual incidence of cirrhosis of 8–10%. Refer to section on *Liver transplantation*. For more information on cirrhosis, refer *to Notes for Guidance for gastroenterological conditions*.

Typical costs are given in Table 15.

Table 15: Scenario 3: Chronic HBV (with/without HBeAg): Annual costs as of April 2019

Service	Item reference	Code	Usual dose/ frequency	Unit cost	Estimated annual cost
Medications					
Entecavir 500 microgram tablet, 30	PBS	10279B	0.5mg oral once daily	179.25	$2,330
Medical					
GP consultation	MBS	23	2 per year	$37.60	$75
Specialist consultation – Treatment and management plan	MBS	132	1 per year	$267.85	$268
Specialist consultations	MBS	116	3 per year	$76.65	$230
Subtotal					$573
Diagnostics					
HBV serology (complete)	MBS	69484	Every 3 months on therapy	$17.10	$68
HBV DNA	MBS	69482	Every 3 months on therapy	$152.10	$608
FBC	MBS	66512	3-monthly	$17.70	$71
ALT	MBS	66500	Every 4 months	$9.70	$29
AFP	MBS	66650	Every 6 months	$24.35	$49
Bone densitometry (in presence of chronic liver disease)	MBS	12315	Annual	$102.40	$102
Ultrasound	MBS	55037	Every 6 months if CHB	$37.85	$76
Subtotal					$1,003
Total					**$ 3,906**
Unit values are presented up to 2 decimal places. Total costs have been computed on these unit values, and rounded to the nearest whole number or to the nearest whole number of full pack size costs.					

Scenario 4: Chronic hepatitis C with positive HCV RNA

A 44-year-old patient was diagnosed with HCV in 1999 and has probably been infected with the virus since the early 1990s after a period of injection equipment sharing. The patient currently reports being easily fatigued with skin rashes intermittently and had elevated liver enzymes on a number of occasions. HCV antibody test is positive and liver enzyme tests have been abnormal on recent and previous testing with an ALT of 70–80 U/L. There is no evidence of liver synthetic function abnormality, with albumin, prothrombin and platelets in the normal range. The patient is HCV genotype 2 with a viral load of 1.2 x 10^6 IU/mL. A liver biopsy shows mild-to-moderate fibrosis without cirrhosis or bridging fibrosis.

Clinical opinion

Assuming that the patient wasn't treated previously, the recommended treatment regimen for genotype 2 is either glecaprevir + pibrentasvir for 8 weeks or sofosbuvir + velpatasvir for 12 weeks.

Typical costs are given in Table 16

Table 16: *Scenario 4: Chronic HCV: Annual costs as of April 2019*

Description	Item reference	Code	Frequency	Unit cost	Annual costs
Medication: HCV genotype 2					
Glecaprevir 100 mg + pibrentasvir 40 mg film-coated tablet, 84	PBS	11344C	orally 3 tablets daily for 8 weeks	$18,817.71	$37,635
Medical					
GP consultation	MBS	23	2 per year	$37.60	$75
Specialist consultation – treatment and management plan	MBS	132	1 per year	$267.85	$268
Specialist consultations (whilst on therapy)	MBS	116	8 per year	$76.65	$613
Subtotal					$956
Diagnostics					
HCV RNA	MBS	69445	Initial assessment every 3 months on therapy and post-therapy	$92.20	$461
HCV genotype	MBS	69491	Initial assessment	$204.80	$205
FBC; liver function test; electrolytes and BGL	MBS	66512	Initial assessment of CHC, and monthly for 6 months on therapy	$17.70	$124

Description	Item reference	Code	Frequency	Unit cost	Annual costs
Coagulation profile	MBS	65120	Initial assessment of CHC	$13.70	$14
Plasma TSH	MBS	66719	Initial assessment of CHC, and monthly for 6 months on therapy	$34.80	$244
Quantitation of HCV RNA load in the pretreatment evaluation by specialist	MBS	69478	6-month intervals	$29.25	$59
Subtotal					$1,107
Total					**$39,638**

Unit values are presented up to 2 decimal places. Total costs have been computed on these unit values, and rounded to the nearest whole number or to the nearest whole number of full pack size costs.

Scenario 5: End-stage liver disease, including transplantation

A 58-year-old patient was diagnosed with HCV in 1993 after having acquired the infection in the early 1970s. The patient has been unwell over the past 3 years, with episodes of jaundice, haematemesis, ascites and ankle swelling. Her platelets are 67 and INR is 1.9. Previous endoscopy has shown oesophageal varices and ultrasound demonstrated a nodular liver with evidence of portal hypertension and mild ascites.

Clinical opinion

The cumulative 5-year survival rate once decompensated cirrhosis ensues is 35%.

This patient shows clear evidence of decompensation of chronic liver disease. likely related to chronic hepatitis C. She has portal hypertension, deranged hepatic synthetic function and thrombocytopenia. Supportive treatment for ESLD includes diuretics, dietary salt-restriction and increased protein intake, management of hepatic encephalopathy and endoscopy with endoscopic variceal ligation of oesophageal varices, if needed. Antiviral therapy for chronic hepatitis C may be undertaken, and ongoing surveillance for liver lesions suggestive of hepatocellular carcinoma should take place every six months at minimum.

Risk of bleeding from oesophageal varices is generally 5–15% per year, with a mortality of 20% at 6 weeks. However, risk of re-bleeding after an acute gastrointestinal haemorrhage for this patient is around 60% within 1–2 years if untreated, and about 32% (median) in patients treated with endoscopic variceal ligation (EVL). Multiple EVLs may be required based upon the clinical need in the acute setting; usually, 7–14 daily (on average 2–4 sessions) until variceal obliteration, and 3–6 monthly pharmacotherapy with a non-selective beta-blocker such as propranolol with or without a nitrate, for example isosorbide mononitrate. This is often used in combination with EVL for secondary prophylaxis of variceal bleeding.

Diuresis should be escalated whilst maintaining pathologic monitoring for any decline in renal function or hyperkalaemia (that may complicate the diuretic use) until the patient has no clinical features of fluid overload, so as to minimise the risk of acute perioperative complications. Recurrent abdominal paracenteses may be required, sometimes even up to weekly occurrences for management of symptomatic ascites, such as dyspnoea or abdominal pain. Treatment of intercurrent skin and soft tissue infections, especially cellulitis of the lower limbs, may be required with antibiotics, usually as an outpatient.

The patient is likely to require vitamin K and blood product support around the time of procedures and in the event of clinically apparent bleeding.

This patient is likely to be evaluated for liver transplantation due to decompensated cirrhosis from HCV. A few specific points that should also be considered are listed below.

- The frequency of endoscopy required to monitor oesophageal varices and the use of pharmacological prophylaxis will be dependent upon the endoscopic findings.
- ICU and high-dependency unit beds are often required for such patients during episodes of decompensation, though this is relatively unpredictable.
- Frequency of consultations and blood test monitoring will be high and dependent upon the degree of abnormality and response to therapy.

If HCV treatment was not undertaken prior to transplant, or SVR was not achieved, treatment of the infection post-transplant should take place.

The median patient survival for this patient is around 15-20 years and hence the duration of costings could reasonably be 15 years for this patient. Graft survival appears fairly similar.

Table 17: Scenario 5: End-stage liver disease, including transplantation: 10-year costs as of April 2019

Service	Item reference	Code	Unit cost	Pre-transplant		Year of transplant		Post-transplant	
				Frequency	Estimated cost for 4 months	Frequency	Estimated annual cost	Frequency	Estimated cost for 9 years
Medical									
GP consultation	MBS	23	$37.60	Monthly	$150	9	$338	2 per year	$677
Specialist consultation – Treatment and management plan	MBS	132	$267.85	once	$268	-	-	-	-
Specialist consultations	MBS	116	$76.65	10	$767	18 (weekly to week 6, second-weekly to week 12, monthly to 12 months, and 3-monthly thereafter)	$1,380	4 per year	$2,759
Dietary consultation	MBS	10954	$62.25	-	-	2	$125	Annual	$560
Subtotal					$1,185		$1,843		$3,996
Diagnostics									
Biochemistry; FBC	MBS	66512	$17.70	Fortnightly	$142	Weekly to week 6, second-weekly to week 12, monthly to 12 months, and 3- monthly thereafter	$850	4 per year	$637

Service	Item reference	Code	Unit cost	Pre-transplant		Year of transplant		Post-transplant	
				Frequency	Estimated cost for 4 months	Frequency	Estimated annual cost	Frequency	Estimated cost for 9 years
Prothrombin time/INR						Monthly		Monthly annually	
CMV viral load	MBS	69384	$15.65	-	-	Annual	$16	Annual	$141
Abdominal paracentesis	MBS	30406	$52.20	4	$209	-	-	-	-
Ultrasound	MBS	55036	$111.30	-	-	1 at 2–4 weeks post-transplant, then as needed (assume 2)	$223	Annual	$1,002
CT scan	MBS	61361	$461.40	-	-	Once	$461	-	-
MRI	MBS	63482	$403.20	-	-	Once	$403	-	-
Liver biopsy	MBS	30409	$174.45	-	-	2	$349	2 per year	$3,140
Bone density scanning	MBS	12306	$102.40	-	-	Annual	$102	Annual	$922
Subtotal					$351		$2,404		$5,842
Pharmaceutical									
Glecaprevir 100 mg + pibrentasvir 40 mg film-coated tablet, 84	PBS	11344C	$18,817.71	orally 3 tablets daily	$37,635	-	-	-	-

Service	Item reference	Code	Unit cost	Pre-transplant		Year of transplant		Post-transplant	
				Frequency	Estimated cost for 4 months	Frequency	Estimated annual cost	Frequency	Estimated cost for 9 years
Spironolactone 25 mg tablet, 100	PBS	2339D	$16.35	25 mg daily	$33	-	-	-	-
Furosemide (frusemide) 20 mg tablet, 50	PBS	1810G	$6.51	20 mg daily	$20	-	-	-	-
Propranolol hydrochloride 10 mg tablet, 100	PBS	2565B	$14.08	10 mg daily	$28	-	-	-	-
Trimethoprim 160 mg + sulfamethoxazole 800 mg tablet, 10	PBS	2951H	$13.22	-	-	1 tablet 3 times per week	$212	-	-
Valganciclovir 450 mg tablet, 60	PBS	6357N	$1,064.53	-	-	900 mg daily for 3–6 months (prevention of CMV infection)	$6,387	-	-
Intravenous methylprednisolone and/or oral prednisone		Table 12	Table 12	-	-	200 mg first day, reducing to 20 mg daily from days 7–30, 15 mg daily to day 60, 10 mg daily to day 90, then 5 mg daily single dose	$169	5 mg daily	$783
Prednisone 5 mg tablet, 60	PBS	1935W	$12.34						

Service	Item reference	Code	Unit cost	Pre-transplant		Year of transplant		Post-transplant	
				Frequency	Estimated cost for 4 months	Frequency	Estimated annual cost	Frequency	Estimated cost for 9 years
Tacrolimus		Table 12	Table 12	-	-	Table 12	$4,085	Table 12	$36,765
Azathioprine		Table 12	Table 12	-	-	Table 12	$258	Table 12	$2,322
Additional post-transplant medications for management of various comorbid issues		-	-	-	$200	-	$200	-	$1,800
Subtotal					$37,916		$11,311		$41,670
Hospital									
Other contacts with health services, with endoscopy	DRG	Z40Z	$1,612	5	$8,060	-	-	-	-
Other disorders of liver, Major complexity	DRG	H63A	$13,725	1	$13,725	1	$13,725	1	$13,725
Other disorders of liver, Intermediate complexity	DRG	H63B	$4,534	4	$18,136	1	$4,534	3	$13,602
Liver transplant	DRG	H09Z	$166,134	-	-	1	$166,134	-	-
Outpatient transplant clinic	Table 11	Table 11	$553	-	-	-	-	9	$4,977

Service	Item reference	Code	Unit cost	Pre-transplant		Year of transplant		Post-transplant	
				Frequency	Estimated cost for 4 months	Frequency	Estimated annual cost	Frequency	Estimated cost for 9 years
Subtotal					$39,921		$184,393		$32,304
Total				**$79,373**		**$199,951**		**$83,812**	
TOTAL 10-YEAR COSTS				**$363,136**					
Unit values are presented up to 2 decimal places. Total costs have been computed on these unit values, and rounded to the nearest whole number or to the nearest whole number of full pack size costs.									

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