HCV in Children:
Australian Commentary on AASLD-IDSA Guidance

This document provides Australian (AU) Commentary on the AASLD-IDSA HCV Guidance: HCV in Children. Recommendations for testing, managing, and treating hepatitis C.

The Australian (AU) Commentary was written by a Committee of Australian paediatric and hepatitis C experts which included representatives from the Gastroenterological Society of Australia (GESA), the Australasian Society for Infectious Diseases (ASID), Hepatitis Australia and Primary Care. The committee was convened and supported by the Australasian Society for HIV, Viral Hepatitis and Sexual Health Medicine (ASHM).*

AU Commentary is only provided where needed in order to provide clarification or detail variations found in the Australian setting.

This document will be reviewed and updated following revision of the AASLD-IDSA guidelines HCV in Children, or when indicated due to nuances in Australia.

Please read the Disclaimer to HCV in Children: Australian Commentary on AASLD-IDSA Guidance.‡

This commentary was last updated in October 2021.

ASID
GESA Gastroenterological Society of Australia
AUSTRALASIAN HEPATOLOGY ASSOCIATION
hepatitis australia
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Testing

Recommendations for HCV Testing of Perinatally Exposed Children and Siblings of Children With HCV Infection	
Recommended	**Rating**
All children born to HCV-infected women should be tested for HCV infection. Testing is recommended using an antibody-based test at or after 18 months of age. **AU COMMENTARY:** **Recommend HCV antibody test from 12-18 months of age and request reflexive testing wherever possible to minimise occasions of venepuncture.**	I, A
Testing with an HCV-RNA assay can be considered in the first year of life, but the optimal timing of such testing is unknown	IIa, C
Testing with an HCV-RNA assay can be considered as early as 2 months of age. **AU COMMENTARY:** **Infants and children at risk of vertical HCV transmission may be lost to follow up before 18 months of age. HCV-RNA testing during infancy from 8 weeks of age may enable early identification and early referral to a paediatric hepatology or infectious diseases clinic for appropriate follow up.** **HCV RNA testing in this instance satisfies MBS criteria (Item number 69499).**	IIa, B
Repetitive HCV RNA testing prior to 18 months of age is not recommended. **AU COMMENTARY:** **If RNA test is negative at 8 weeks, consider a repeat RNA test after 3 mths if potential loss to follow up.**	III, A
Children who are anti-HCV positive after 18 months of age should be tested with an HCV-RNA assay after age 3 to confirm chronic hepatitis C infection. **AU COMMENTARY:** **This recommendation reflects the fact that children may spontaneously clear infection in the first 3 to 4 years of life, however in the Australian setting, we do not routinely recommend waiting until after age 3 for HCV RNA testing.**	I, A
The siblings of children with vertically-acquired chronic HCV should be tested for HCV infection, if born from the same mother.	I, C

Although the prevalence of chronic hepatitis C is lower in children than adults, an estimated 3.5 to 5 million children worldwide have chronic HCV infection (Indolphi, 2019); (Gower, 2014). Data from the National Health and Nutrition Examination Survey (NHANES) indicate that 0.2% of 6- to 11-year-olds (31,000 children) and 0.4% of 12- to 19-year-olds (101,000 adolescents) in the US are HCV antibody positive (Alter, 1999).

As birth to a woman with chronic hepatitis C is a known risk for infection, children born to these women should be evaluated and tested for HCV. The rate of mother-to-child transmission (MTCT) of HCV infection is approximately 5%, although rates are higher among women with inadequately controlled HIV coinfection, and women with higher HCV-RNA levels, (>6 log10 IU/mL) (Benova, 2014); (Delotte, 2014); (Cottrell, 2013); (Shebl, 2009). Identifying, following, and treating exposed children is recommended. The preferred assay for evaluation of HCV infection early in life is HCV-RNA testing, as maternal antibodies and consequently anti-HCV assay positivity may persist for 18 months (Aniszewska, 2012); (England, 2005). About 25% to 50% of infected infants spontaneously resolve HCV infection (loss of previously detectable HCV RNA) by 4 years of age (Indolfi, 2019); (Garazzino, 2014); (Farmand, 2012); (Yeung, 2007); (EPHCVN, 2005); (Mast, 2005).

There is considerable debate about the utility of HCV-RNA testing within the first year of life. Proponents argue that use of a highly sensitive RNA assay early in life can increase the rate of infected infants detected, and that a negative result strongly suggests the infant is not infected while a positive result helps identify HCV cases earlier. Proponents also want to seize opportunity to test in a patient group that is often lost to follow-up. Opponents argue that early testing does not change the need for definitive testing at or after 18 months; HCV RNA is more expensive than an antibody-based test; and there is no intervention or treatment that will occur prior to age 3—because of lack of approved drugs for this age group and to allow for possible spontaneous clearance. One large single center study demonstrated that HCV-RNA testing done in exposed infants aged 2 months to 6 months led to reliable positive and negative results that correlated with ultimate testing at 18 months (Honegger, 2018). There is no value in repeated HCV-RNA testing prior to 18 months of age, but anti-HCV testing should take place at or after 18 months of age.

AU COMMENTARY:

Only 16-45% of infants at risk of vertical transmission of HCV infection are appropriately tested, suggesting that follow up of these infants can be difficult (Kuncio, 2016; Watts, 2017; Chappell, 2018; Epstein, 2018; Towers, 2019; Lopata, 2020). The value of HCV RNA testing from 2 months of age was demonstrated in the largest of these studies where 41% of infected children were identified by this method; 48% were identified by HCV-antibody testing from 18 months, and 11% received both tests (Lopata, 2020).

We recommend early testing with HCV RNA PCR from 2 months of age, to enable identification and engagement with a paediatric gastroenterology or infectious disease service, particularly where there is a risk of loss to follow up before 18 months of age.

Less-invasive testing techniques, such as point-of-care finger-stick sampling of blood or dried blood spot testing, should be utilised where feasible to limit distress for patients, parents and carers.

Counselling should be provided to the parents and/or family. Mothers whose babies acquire HCV through vertical transmission have a lower quality of life compared with mothers without HCV infection (Rodrigue, 2009).

Transmission and Prevention

Recommendations for Counseling Parents Regarding Transmission and Prevention in Children with HCV Infection	
Recommended	**Rating**
Parents should be informed that hepatitis C is not transmitted by casual contact and, as such, children with HCV infection do not pose a risk to other children and can participate in school, sports, and athletic activities, and engage in all other regular childhood activities without restrictions.	I, B
Parents should be informed that universal precautions should be followed at school and in the home of children with HCV infection. Educate families and children about the risk and routes of HCV transmission, and the techniques for avoiding blood exposure, such as avoiding the sharing of toothbrushes, razors, and nail clippers, and the use of gloves and dilute bleach to clean up blood.	I, B

HCV-infected children often face discrimination and stigmatization in school and child-care settings that is driven by public misunderstanding regarding hepatitis C transmission. HCV is not transmitted by casual contact in the absence of blood exposure. Families should not be forced to disclose a child's HCV infection status, and children should not be restricted from any routine childhood activity.

The risk of sexual transmission of hepatitis C is considered very low/rare. Sexual transmission occurs but is generally inefficient except among HIV-infected men who have unprotected sex with men (see HCV Testing and Linkage to Care) (Tieu, 2018); (Vaux, 2019); (Schmidt, 2014). Adolescents with HIV infection and those with multiple sexual partners or sexually transmitted infections (STIs) should be encouraged to use barrier precautions to prevent sexual transmission of HCV and other STIs. Other adolescents with HCV infection should be counseled that the risk of sexual transmission is low but barrier precautions are recommended for other reasons (see Testing and Linkage to Care: Table 2 - Measures to Prevent Transmission of HCV).

AU COMMENTARY:

Perinatal transmission is the most common mode of HCV transmission for children (Jhaveri, 2014). The overall risk of perinatal transmission in HIV-negative pregnant women is 5.8% and in HCV/HIV co-infected pregnant women 10.8% (Benova, 2014). The risk of perinatal transmission is not affected by mode of delivery, but increases with premature rupture of membranes and invasive fetal monitoring (Ghamar Chehreh, 2011); (Mast, 2005). Breastmilk feeding has not been shown to increase the risk of HCV transmission, though avoidance of breastmilk feeding should be considered if the mother has cracked and bleeding nipples.

Guidance on the management of HCV in pregnancy including the prevention of perinatal transmission are available through The Royal Australian and New Zealand College of Obstetricians and Gynaecologists (https://ranzcog.edu.au/RANZCOG_SITE/media/RANZCOG-MEDIA/Women%27s%20Health/Statement%20and%20guidelines/Clinical-Obstetrics/Management-of-Hepatitis-C-in-Pregnancy-(C-Obs-51).pdf?ext=.pdf), ASHM (https://www.ashm.org.au/HCV/), and ASID (https://www.asid.net.au/documents/item/368).

Mothers with HCV should be provided with supportive information and linkage to care, including counselling around disclosure related issues. Parents/carers should also be counselled to disclose their child's HCV status to them at an appropriate time.

Monitoring and Medical Management

Recommendations for Monitoring and Medical Management of Children With HCV Infection	
Recommended	**Rating**
Routine liver biochemistries at initial diagnosis and at least annually thereafter are recommended to assess for disease progression. **AU COMMENTARY:** **Annual HCV PCR testing is recommended, especially in the first 5 years of life given the reported rates of spontaneous viral clearance in these children.**	I, C
Appropriate vaccinations are recommended for children with chronic HCV infection who are not immune to hepatitis B virus and/or hepatitis A virus to prevent these infections.	I, C
Disease severity assessment via routine laboratory testing and physical examination, as well as use of evolving noninvasive modalities (ie, elastography, imaging, or serum fibrosis markers) is recommended for all children with chronic HCV infection.	I, B
Children with cirrhosis should undergo hepatocellular carcinoma (HCC) surveillance and endoscopic surveillance for varices per standard recommendations.	I, B
Hepatotoxic drugs should be used with caution in children with chronic HCV infection after assessment of potential risks versus benefits of treatment. Use of corticosteroids, cytotoxic chemotherapy, and/or therapeutic doses of acetaminophen are not contraindicated in children with chronic HCV infection.	II, C
Solid organ transplantation and bone marrow transplantation are not contraindicated in children with chronic HCV infection.	II, C
Anticipatory guidance about the potential risks of ethanol for progression of liver disease is recommended for adolescents with chronic HCV infection and their families. Abstinence from alcohol and interventions to facilitate cessation of alcohol consumption, when appropriate, are advised for all persons with chronic HCV infection.	I, C
AU COMMENTARY: **Additional recommendation: Children with chronic hepatitis C should be supported to maintain a healthy body weight to avoid liver related complications of obesity such as steatohepatitis, as well as the known deleterious effects of insulin resistance on fibrosis progression with HCV infection.**	**1, C**

Liver disease due to chronic HCV infection generally progresses slowly in children, and cirrhosis and liver cancer occur infrequently. Although elevated serum aminotransferase levels are often noted, HCV-infected children younger than 3 years virtually never develop advanced liver disease.

AU COMMENTARY:
Young children with HCV almost never develop advanced liver disease. There are some cases of rapid fibrosis rate in adolescents leading to cirrhosis (Guido, 1998); (Guido, 2003); (Pham 2016).

The initial assessment of children with chronic HCV infection includes exclusion of other causes of liver disease, assessment of disease severity, and detection of extrahepatic manifestations. Testing for concomitant HBV (HBsAg, anti-HBc, and anti-HBs), HIV (anti-HIV), and immunity to HAV (anti-HAV IgG) are recommended due to shared risk factors and the need to vaccinate nonimmune children who may not have received routine childhood HAV and HBV vaccines.

AU COMMENTARY:
Consider referral to a paediatric gastroenterologist for other causes of liver disease.

Disease staging in children can be accomplished via physical examination and assessment of routine laboratory parameters including albumin, serum hepatic aminotransferase levels, total bilirubin, international normalized ratio (INR), and platelet count every 6 to 12 months. Serum fibrosis markers also hold promise to stratify disease severity but require further validation (Nielsen, 2019); (Pokorska-Spiewak, 2017); (Mack, 2012). Of note, serum aminotransferase levels are not consistently reflective of disease severity in children. In one study, nearly 33% of children had normal aminotransferase levels despite substantial necroinflammation on biopsy (Casiraghi, 2004).

AU COMMENTARY:
Children up to the age of 4 are reported to spontaneously clear HCV in 25 to 50% of cases (Indolfi, 2019); (Garrazino, 2014); (Farmand, 2012); (Yeung, 2007); (EPHCVN, 2005); (Mast, 2005). Annual PCR testing for this age group will identify those children who have successfully resolved their HCV infection.

For children in whom advanced liver disease is a concern, liver imaging to evaluate for splenomegaly or venous collaterals is recommended initially, using liver ultrasound instead of CT or MRI due to its widespread availability and lack of ionizing radiation. Although liver biopsy is considered the gold standard regarding the grade of inflammation and stage of fibrosis, sampling artifact is problematic and most patients and practitioners prefer noninvasive alternatives, such as liver elastography, to determine the presence/absence of cirrhosis, particularly in children. Ultrasound-based liver elastography in children requires the use of specialized probes and cutoff values for advanced fibrosis/cirrhosis that differ from those used in adults, but this approach appears promising for monitoring children with chronic HCV infection (Behairy, 2016); (Geng, 2016); (Lee, 2013).

Due to the slow rate of fibrosis progression among children, there are few, if any, established bona fide risk factors for disease progression. Development of advanced liver disease in children is infrequent until more than 30 years of infection (Jhaveri, 2011); (Goodman, 2008); (Minola, 2002). However, as in adults, children with comorbid disease—such as obesity with nonalcoholic fatty liver disease and congenital heart disease with elevated right heart pressures—and those receiving hepatotoxic drugs should be monitored carefully for disease progression.

AU COMMENTARY:
Any comorbid liver disease, eg alpha-1 antitrypsin deficiency, may require more careful monitoring. Consider referral to a paediatric gastroenterologist.

Hepatocellular carcinoma (HCC) is rarely encountered among children and has been reported almost exclusively in those with cirrhosis. There are reports that children with chronic HCV infection and a history of childhood leukemia may be at increased risk of developing HCC but evidence is limited (González-Peralta, 2009). In children with cirrhosis, liver ultrasound with or without serum alpha-fetoprotein (AFP) testing every 6 months is recommended

for HCC surveillance per AASLD guidelines (Marrero, 2018). A baseline endoscopy is advisable to detect esophageal varices in children with cirrhosis and every 3 years thereafter in the absence of viral clearance. After successful antiviral therapy, the risk for cirrhosis complications decreases substantially.

In children with advanced fibrosis from chronic HCV infection, medications that are known to accelerate hepatic fibrosis (eg, methotrexate) should be avoided, if possible. Similarly, abstinence from alcohol use is strongly advised to minimize disease progression. Although corticosteroids and other immunosuppressants may enhance HCV replication, they are not contraindicated in children with HCV infection and should be prescribed for appropriate indications based on overall risks versus benefits. Of note, icteric flares of HCV—as reported in children and adults with chronic HBV—have not been reported in children receiving an organ transplant or cytotoxic chemotherapy. Although underlying liver disease is a risk factor for development of sinusoidal obstruction syndrome following bone marrow transplantation, the presence of HCV infection should not delay this therapy.

To remain well, untreated children with chronic hepatitis C are encouraged to maintain a healthy body weight due to the known deleterious effects of insulin resistance on fibrosis progression with HCV infection (Kukla, 2015); (Petta, 2011); (Cua, 2008); (Moucari, 2008). Commonly used medications, such as antimicrobial agents, antiepileptics, and cardiovascular agents, should be dosed per standard recommendations. However, nonsteroidal anti-inflammatory drugs and aspirin should be avoided, if possible, in children with cirrhosis and esophageal varices due to concerns of gastrointestinal bleeding and nephrotoxicity. Acetaminophen is a safe and effective analgesic for children with chronic HCV infection when dosed per package insert recommendations.

AU COMMENTARY:

Paracetamol is a safe and effective analgesic for children with chronic HCV infection when dosed per package insert recommendations.

Whom and When to Treat Among Children and Adolescents With HCV Infection

AU COMMENTARY:

Children and adolescents with chronic hepatitis C should be managed by a paediatric gastroenterologist or infectious diseases specialist with experience in this condition. These medications have side effects and drug-drug interactions which need to be monitored.

Any child or adolescent with proven or suspected cirrhosis and hepatitis C should be referred to a paediatric gastroenterologist for ongoing management.

Test all patients for evidence of current or prior HBV infection by measuring hepatitis B surface antigen (HBsAg) and hepatitis B core antibody (anti-HBc) before initiating HCV treatment. Hepatitis B virus (HBV) reactivation has been reported in HCV/HBV coinfected patients who were undergoing or had completed treatment with HCV direct acting antivirals, and who were not receiving HBV antiviral therapy. Some patients developed fulminant hepatitis, hepatic failure, and death. Cases have been reported in patients who are HBsAg positive and also in patients with serologic evidence of resolved HBV infection (i.e., HBsAg negative and anti-HBc positive).

Recommendations for Whom and When to Treat Among Children and Adolescents With HCV Infection	
Recommended	**Rating**
Direct-acting antiviral (DAA) treatment with an approved regimen is recommended for all children and adolescents with HCV infection aged ≥3 years as they will benefit from antiviral therapy, regardless of disease severity. **AU COMMENTARY:** **Treatment can be considered from the age of 3, however may be delayed until the age of 6 taking into account various considerations including: the chance of spontaneous clearance, patient and family factors, patient weight and available formulations.** **Currently, ONLY fixed dose formulations are available which restricts use to certain weight categories as below.**	I, B
The presence of extrahepatic manifestations—such as cryoglobulinemia, rashes, and glomerulonephritis—as well as advanced fibrosis should lead to early antiviral therapy to minimize future morbidity and mortality.	I, C

HCV-related, advanced liver disease is uncommon during childhood. However, liver disease progresses over time with increasing fibrosis severity (Indolfi, 2019); (Mizuochi, 2018); (Bortolotti, 2008); (EPHCVN, 2005); (Resti, 2003). Although uncommon, cirrhosis occurs occasionally in children and adolescents (aged <18 years) with HCV infection. Children have a long life expectancy during which HCV complications may develop. Children and adolescents with HCV infection may also transmit the virus to others.

The high success rates with DAA regimens in adults with chronic HCV infection are increasingly being replicated in the pediatric population. Interferon and ribavirin exert general and pediatric-specific toxicities (eg, temporary growth impairment) that do not occur with DAA regimens. Additionally, interferon-based regimens have limited success

in children and adolescents with genotype 1 or 4. Promising early and emerging clinical trial data evaluating DAA regimens in children and adolescents usher in the opportunity to expand use of these safe, well-tolerated, efficacious HCV therapies in the pediatric population.

Treatment of children as young as 12 years is predicted to be very cost-effective with currently approved DAA regimens as well as those in clinical trials (Nguyen, 2019b). Another cost-utility analysis compared DAA treatment at age 6 versus delaying treatment until age 18. The researchers reported the incremental cost-utility ratio for early vs delayed DAA therapy was <$12,000 per QALY gained. They concluded that treatment during early childhood is cost-effective and delaying therapy until early adulthood may result in increased lifetime risk of complications of late-stage liver disease (Greenway, 2019). FDA-approved DAA regimens are available for children aged 3 to <18 years with genotype 1, 4, 5 or 6 infection and for children aged 6 to <18 years with any HCV genotype.

AU COMMENTARY:

Children and adolescents with HCV require counselling and education to understand the risk of transmission, measures to protect themselves and others and disclosure related issues.

Education by parents should be provided in partnership with paediatric hepatology/infectious diseases staff (nursing, social worker/psychologist and medical consultants).

In April 2020, the PBS removed the age restrictions for all DAA regimens currently approved for adults. We recommend however that only regimens which have been shown in paediatric trials to be effective in children be used. As weight-based dosing in crucial to success, the availability of single formulations currently in Australia further restrict which children can be treated. These combinations are highlighted in the tables and commentary below.

Testing for resistance associated variants should be considered in the event of DAA treatment failure to help guide future therapy.

HCV Antiviral Therapy for Children and Adolescents, Without Cirrhosis or With Compensated Cirrhosis (Child-Pugh A)

Recommended regimens listed by age: **Treatment-Naive or Interferon-Experienced Children and Adolescents Without Cirrhosis or With Compensated Cirrhosis[a]**		
Recommended	**Duration**	**Rating**
Combination of ledipasvir/sofosbuvir (weight-based dosing; see Table 1) for children aged ≥3 years with genotype 1, 4, 5, or 6 **AU COMMENTARY:** **The only formulation available in Australia is fixed-dose combination ledipasvir (90mg)/sofosbuvir (400mg). This dosing allows adolescents ≥12 years and ≥35kg to be treated. Note that treatment of children <18 years is not included in the product label in Australia.**	12 weeks	I, C
Combination of sofosbuvir/velpatasvir (weight-based dosing; see Table 2) for children aged ≥6 years or weighing ≥17 kg with any genotype **AU COMMENTARY:** **The only formulation available in Australia is fixed-dose combination sofosbuvir (400mg)/ velpatasvir (100mg). This dosing allows adolescents ≥12 years and weighing ≥30kg to be treated.**	12 weeks	I, B
Combination of glecaprevir (300 mg)/pibrentasvir (120 mg) for adolescents aged ≥12 years or weighing ≥45 kg with any genotype **AU COMMENTARY:** **The only formulation available in Australia is fixed-dose glecaprevir (100 mg)/ pibrentasvir (40 mg). No dose adjustment is required in adolescents 12 years and older. In children between 6 and 12 years of age and weight ≥20 kg to <30 kg, treatment may be considered with a reduced dose (2 tablets daily). For children between 6 and 12 years of age and weight ≥30 kg to <45 kg, seek advice from a paediatric gastroenterologist or infectious diseases physician.**	8 weeks	I, B
[a] Child-Pugh A		

Recommended regimens listed by age: **DAA-Experienced Children and Adolescents, Without Cirrhosis or With Compensated Cirrhosis[a]**		
Recommended	**Duration**	**Rating**
Genotype 1: Combination of ledipasvir/sofosbuvir (weight-based dosing; see Table 1) for children and adolescents aged ≥3 years with prior exposure to an interferon (± ribavirin) plus an HCV protease inhibitor regimen, without cirrhosis **AU COMMENTARY:** **The only formulation available in Australia is fixed-dose combination ledipasvir (90mg)/sofosbuvir (400mg). This dosing allows adolescents ≥12 years and ≥35kg to be treated. Note that treatment of children <18 years is not included in the product label in Australia.**	12 weeks	I, C
Genotype 1: Combination of ledipasvir/sofosbuvir (weight-based dosing; see Table 1) for children and adolescents aged ≥3 years with prior exposure to an interferon (± ribavirin) plus an HCV protease inhibitor regimen, with compensated cirrhosis[a] **AU COMMENTARY:** **The only formulation available in Australia is fixed-dose combination ledipasvir (90mg)/sofosbuvir (400mg). This dosing allows adolescents ≥12 years and ≥35kg to be treated. Note that treatment of children <18 years is not included in the product label in Australia.**	24 weeks	I, C
Genotype 4, 5, or 6: Combination of ledipasvir/sofosbuvir (weight-based dosing; see Table 1) for children and adolescents aged ≥3 years with prior exposure to an interferon (± ribavirin) plus an HCV protease inhibitor regimen, without cirrhosis or with compensated cirrhosis[a] **AU COMMENTARY:** **The only formulation available in Australia is fixed-dose combination ledipasvir (90mg)/sofosbuvir (400mg). This dosing allows adolescents ≥12 years and ≥35kg to be treated. Note that treatment of children <18 years is not included in the product label in Australia.**	12 weeks	I, C
Genotype 1, 2, 4, 5, or 6: Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) for adolescents aged ≥12 years or weighing ≥45 kg with prior exposure to an interferon-based regimen (± ribavirin) and/or sofosbuvir but no exposure to NS3/4A or NS5A protease inhibitors, without cirrhosis	8 weeks	I, C
Genotype 1, 2, 4, 5, or 6: Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) for adolescents aged ≥12 years or weighing ≥45 kg with prior exposure to an interferon-based regimen (± ribavirin) and/or sofosbuvir but no exposure to NS3/4A or NS5A protease inhibitors, with compensated cirrhosis[a]	12 weeks	I, C

Genotype 3: Daily fixed-dose combination of glecaprevir (300 mg)/ pibrentasvir (120 mg) for adolescents aged ≥12 years or weighing ≥45 kg with prior exposure to an interferon-based regimen (± ribavirin) and/ or sofosbuvir but no exposure to NS3/4A or NS5A protease inhibitors, without cirrhosis or with compensated cirrhosis[a]	16 weeks	I, C
Genotype 1: Daily fixed-dose combination of glecaprevir (300 mg/ pibrentasvir (120 mg) for adolescents aged ≥12 years or weighing ≥45 kg with prior exposure to NS3/4A protease inhibitors but no NS5A inhibitor exposure, without cirrhosis or with compensated cirrhosis[a]	12 weeks	I, C
Genotype 1: Daily fixed-dose combination of glecaprevir (300 mg)/ pibrentasvir (120 mg) for adolescents aged ≥12 years or weighing ≥45 kg with prior exposure to an NS5A inhibitor but no NS3/4A protease inhibitor exposure, without cirrhosis or with compensated cirrhosis[a]	16 weeks	I, C
[a] Child-Pugh A		

Ledipasvir/Sofosbuvir

Ledipasvir/sofosbuvir is approved for use in children aged 3 through 17 years with genotype 1, 4, 5, or 6 infection. In a phase 2, multicenter, open-label study of 100 adolescents with genotype 1 treated for 12 weeks with the adult formulation of ledipasvir/sofosbuvir, SVR12 was documented in 98% of participants (Balistreri, 2017). The 2 patients who did not achieve SVR12 were lost to follow-up during or after treatment. Eighty percent of the patients were treatment naive. One patient had cirrhosis, 42 did not, and the cirrhosis status was unknown in the remaining 57. The regimen was safe and well tolerated in this population, and the adult dosage formulation resulted in pharmacokinetic characteristics similar to those observed in adults. Two clinical trials supporting the approval of ledipasvir/sofosbuvir in the pediatric population aged 3 through 11 years demonstrated high SVR12 rates comparable to those seen in adults (Schwarz, 2019); (Murray, 2018). Among children <12 years of age, dosing is weight based (see Table 1). Twelve weeks of ledipasvir/sofosbuvir is recommended for treatment-naive children and adolescents aged ≥3 years without cirrhosis or with compensated cirrhosis (Child-Pugh A). This regimen is also recommended for interferon-experienced (± ribavirin, with or without an HCV protease inhibitor) children and adolescents aged ≥3 years with genotype 1 or 4. A 12-week course is recommended for patients without cirrhosis; 24 weeks is recommended for those with compensated cirrhosis.

The combination of ledipasvir/sofosbuvir is the only treatment option for children with genotype 1, 4, 5, or 6 infection who are 3 to <6 years of age. It is also a good option for older children and adolescents with these genotypes.

Table 1. Weight-Based Dosing of Ledipasvir/Sofosbuvir for Children Aged ≥3 Years

Body Weight	Once Daily Dose of Ledipasvir/Sofosbuvir
<17 kg	33.75 mg/150 mg
17 to <35 kg	45 mg/200 mg
≥35 kg	90 mg/400 mg per day

AU COMMENTARY:

As noted, there is an evidence base for treating children and adolescents with genotype 1,4,5,6 HCV. However, the only formulation available in Australia is daily fixed-dose combination of single tablet ledipasvir (90mg)/sofosbuvir (400 mg), which can be used to treat adolescents ≥12 years and weighing at least 35kg with Genotype 1, 4-6 hepatitis C.

Note: the Australian product label has not yet been updated to include this.

Sofosbuvir/Velpatasvir

The efficacy of sofosbuvir/velpatasvir once daily for 12 weeks was evaluated in an open-label trial among 173 pediatric participants aged ≥6 years with genotype 1, 2, 3, 4, or 6 infection, without cirrhosis or with compensated cirrhosis. Eighty-five percent of participants (147/173) were treatment naive and 15% (26/173) were treatment experienced. Overall SVR12 was ≥92% across genotypes (Jonas, 2019a).

Among 102 adolescents aged 12 to <18 years, 78% (n=80) were treatment naive and 22% (n=22) were treatment experienced. The median age was 15 years (range 12 to 17 years); 51% were female. The genotype distribution among the participants was 74% genotype 1, 6% genotype 2, 12% genotype 3, 2% genotype 4, and 6% genotype 6. No adolescents had known cirrhosis. The majority (89%; 91/102) had been infected through vertical transmission. SVR12 rates were 93% in adolescents with genotype 1, 91% in those with genotype 3, and 100% in participants with genotype 2, 4, or 6. One participant discontinued treatment at week 4 and subsequently relapsed. The other 4 participants who did not achieve SVR12 did not meet virologic failure criteria (lost to follow-up).

Among 71 children aged 6 to <12 years, the genotype distribution was 76% genotype 1, 3% genotype 2, 15% genotype 3, and 6% genotype 4. None of the participants had known cirrhosis. Ninety-four percent (n=67) were treatment naive and 6% (n=4) 4 were treatment experienced. The median age was 8 years (range 6 to 11 years); 54% were female. The majority of children (94%; 67/71) had been infected through vertical transmission. SVR12 rates were 93% (50/54) in children with genotype 1, 91% (10/11) in those with genotype 3, and 100% in participants with genotype 2 (2/2) or genotype 4 (4/4). One participant had on-treatment virologic failure; the other 4 participants who did not achieve SVR12 did not meet virologic failure criteria (lost to follow-up).

Sofosbuvir/velpatasvir was approved by the FDA for pediatric patients aged ≥6 years in March 2020. Given its pangenotypic activity, safety, and efficacy, sofosbuvir/velpatasvir is recommended as a first choice for HCV treatment in children and adolescents at least 6 years of age. Due to reports from experience among adults, coadministration of sofosbuvir/velpatasvir with amiodarone is not recommended due to the risk for symptomatic bradycardia.

Table 2. Weight-Based Dosing of Sofosbuvir/Velpatasvir for Children Aged ≥6 Years or Weighing ≥17 kg

Body Weight	Once Daily Dose of Sofosbuvir/Velpatasvir
17 kg to <30 kg	200 mg/50 mg
≥30 kg	400 mg/100 mg

AU COMMENTARY:

In June 2021, the FDA approved sofosbuvir/velpatasvir for the treatment of children aged ≥3 years.

However, the only formulation available in Australia is daily fixed-dose combination of single tablet sofosbuvir (400mg)/velpatasvir (100mg) which can be used to treat adolescents ≥12 years and weighing at least 30kg.

Glecaprevir/Pibrentasvir

The daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) was approved for adolescents aged 12 through 17 years in April 2019. In the registration trial, 47 adolescents were treated with the adult-approved coformulated preparation; the duration of treatment was based on viral genotype, prior treatment, and cirrhosis status (Jonas, 2019). Genotypes 1 through 4 were represented in the trial. Two participants were HIV coinfected, none had cirrhosis, and 11 had a prior treatment failure with peginterferon/ribavirin. SVR12 was 100%. The study drugs were well tolerated with no serious adverse events and no drug discontinuations.

Although there are no data from the adolescent population, EXPEDITION-8 evaluated 8 weeks of glecaprevir/pibrentasvir among 343 treatment-naive adults with genotype 1, 2, 3, 4, 5, or 6 and compensated cirrhosis. Overall SVR12 rates were 99.7% (334/335) in the per-protocol population and 97.7% (335/343) in the intention-to-treat population (Brown, 2019). Similarly, FDA approval and HCV guidance panel HCV treatment recommendations for DAA-experienced adolescents are based on clinical trial data from adults (Asselah, 2018b); (Puoti, 2018); (Wyles, 2018); (Zeuzem, 2018); (Forns, 2017).

Given its pangenotypic activity, safety, and efficacy record in adult patients, glecaprevir/pibrentasvir is recommended as a first choice for adolescent HCV treatment. As in adults, coadministration of carbamazepine, efavirenz-containing regimens, and St. John's wort is not recommended since these compounds may decrease concentrations of glecaprevir and pibrentasvir.

AU COMMENTARY:

Pharmacokinetics studies of glecaprevir/pibrentasvir in children showed that pediatric dosages determined to be efficacious were 250 mg glecaprevir + 100 mg pibrentasvir (in children weighing ≥30 kg to <45 kg), 200 mg glecaprevir + 80 mg pibrentasvir (≥20 kg to <30 kg), and 150 mg glecaprevir + 60 mg pibrentasvir (12 kg to <20 kg). One participant, on the initial dose ratio, relapsed by post-treatment week 4; no participants had virologic failures on the final dose ratio of glecaprevir 50 mg/pibrentasvir 20 mg. (Jonas, 2021).

The only formulation available in Australia is fixed-dose glecaprevir (100 mg)/pibrentasvir (40 mg). No dose adjustment is required in adolescents 12 years and older. In children between 6 and 12 years of age and weight ≥20 kg to <30 kg, treatment may be considered with a reduced dose (2 tablets daily). For children between 6 and 12 years of age and weight ≥30 kg to <45 kg, seek advice from a paediatric gastroenterologist or infectious diseases physician.

Note: The Australian product label states the safety and effectiveness of glecaprevir (100 mg)/pibrentasvir (40 mg) in patients younger than 12 years of age have not been established.

Sofosbuvir Plus Ribavirin

In September 2019, the FDA approved weight-based sofosbuvir plus ribavirin (see Table 3) for treatment-naive or interferon-experienced (± ribavirin) children aged ≥3 years with genotype 2 or 3, without cirrhosis or with compensated cirrhosis (Child-Pugh A). A 12-week course is recommended for patients with genotype 2; 24 weeks is recommended for those with genotype 3. The registration trial conducted in children aged 3 to <11 years demonstrated an SVR12 of 98% (Rosenthal, 2020). The use of sofosbuvir plus ribavirin is further supported from clinical trials conducted among adolescents (Wirth, 2017) and adults with genotype 2 or 3 infection (Sulkowski, 2014); (Zeuzem, 2014a); (Jacobson, 2013); (Lawitz, 2013).

Currently, sofosbuvir plus ribavirin remains the only FDA-approved DAA for children 3 through 5 years with genotype 2 or 3 infection. However, recent clinical trials evaluating weight-based dosing of sofosbuvir/velpatasvir (Jonas, 2019a) and glecaprevir/pibrentasvir (Jonas, 2019b) are expected to lead to FDA approval for children beginning at 3 years of age. The HCV guidance panel recommends delaying treatment pending approval of a pangenotypic regimen unless there is a compelling need for immediate antiviral treatment of children aged 3 through 5 years with genotype 2 or 3 infection.

Table 3. Weight-Based Dosing of Ribavirin for Children Aged ≥3 Years

Body Weight	Daily Dose of Ribavirin (divided AM and PM)
<47 kg	15 mg/kg
47 to 49 kg	600 mg
50 to 65 kg	800 mg
66 to 80 kg	1000 mg
>80 kg	1200 mg

AU COMMENTARY:

Sofosbuvir 400 mg tablets were delisted from the PBS on 1 November 2020, however sofosbuvir will remain available on the PBS as a component of other combinations.

AU COMMENTARY:

FIRST-LINE DAA TREATMENT REGIMENS AVAILABLE IN AUSTRALIA FOR CHILDREN/ADOLESCENTS (AUGUST 2021)				
Regimen	**Genotype**	**Pill Burden**	**Indication**	**Treatment duration[1]**
Sofosbuvir 400 mg + Velpatasvir 100 mg	All	1 tablet daily	≥ 12 years and weight ≥ 30 kg	12 weeks
Glecaprevir 100 mg + Pibrentasvir 40 mg	All	3 tablets once daily	≥ 12 years and weight ≥ 45 kg	8 weeks
		2 tablets once daily	≥ 6 years to < 12 years and weight ≥ 20 kg to < 30 kg[2,3]	8 weeks

[1] Treatment naïve without cirrhosis or with compensated cirrhosis, others see full text

[2] Jonas, 2021

[3] For children ≥ 6 years to < 12 years and weight ≥ 30 kg to < 45 kg, seek advice from a paediatric gastroenterologist or infectious diseases physician.

Rating System Used to Rate Level of Evidence and Strength of Recommendation

Recommendations are based on scientific evidence and expert opinion. Each recommended statement includes a Roman numeral (I, II, or III) representing the level of the evidence that supports the recommendation and a letter (A, B, or C) representing the strength of the recommendation.

Class	
I	Evidence and/or general agreement that a given diagnostic evaluation, procedure, or treatment is beneficial, useful, and effective.
II	Conflicting evidence and/or a divergence of opinion about the usefulness and efficacy of a diagnostic evaluation, procedure, or treatment.
IIa	Weight of evidence and/or opinion is in favor of usefulness and efficacy.
IIb	Usefulness and efficacy are less well established by evidence and/or opinion.
III	Conditions for which there is evidence and/or general agreement that a diagnostic evaluation, procedure, or treatment is not useful and effective or if it in some cases may be harmful.

Level	
A	Data derived from multiple randomized clinical trials, meta-analyses, or equivalent.
B	Data derived from a single randomized trial, nonrandomized studies, or equivalent.
C	Consensus opinion of experts, case studies, or standard of care.

Commonly Used Abbreviations

Abbreviation	Definition and Notes
AASLD	American Association for the Study of Liver Diseases
AFP	alpha-fetoprotein
Anti-HCV	HCV antibody
DAA	direct-acting antiviral
FDA	US Food and Drug Administration
HBsAg	hepatitis B virus surface antigen
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCV	hepatitis C virus Hepatitis C virus and HCV refer to the virus. Hepatitis C and HCV infection or HCV disease refer to the disease entity.
IDSA	Infectious Diseases Society of America
INR	international normalized ratio
NASH	nonalcoholic steatohepatitis
NS3	HCV nonstructural protein 3
NS5A	HCV nonstructural protein 5A
PCR	polymerase chain reaction
QALY	quality-adjusted life-year
RNA	ribonucleic acid
sAg	surface antigen
SVR12 (or 24 or 48, etc)	sustained virologic response at 12 weeks (or at 24 weeks, or at 48 weeks, etc)

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While the Australian Department of Health provided financial support for the HCV in Children: Australian commentary on AASLD-IDSA Guidance, the material contained in this resource should not be taken to represent the views of the Australian Department of Health.

These guidelines are up to date at the time of writing.

AU Commentary Paediatric Guidelines Committee Membership

Name	Role	Affiliation
Prof. Winita Hardikar	Director, Department of Gastroenterology	Royal Children's Hospital Melbourne, Victoria
Prof. Alex Thompson	Director, Department of Gastroenterology	St Vincent's Hospital Melbourne, Victoria
Dr Brett Ritchie	Paediatric Infectious Diseases Specialist	Royal Adelaide Hospital Adelaide, South Australia
Dr Michael Stormon	Senior Staff Specialist Head of Department of Gastroenterology	Children's Hospital Westmead Sydney, NSW
A/Prof Julia Clark	Paediatric Infectious Disease Specialist	Queensland Childrens Hospital South Brisbane, QLD
Dr Adam Bartlett	Paediatric Infectious Diseases Physician	Sydney Children's Hospital Randwick, NSW
Dr Brendan McMullan	Paediatric Infectious Diseases Specialist & Microbiologist	Sydney Children's Hospital Randwick, NSW
Dr Scott Nightingale	Paediatric Gastroenterologist and Hepatologist	John Hunter Children's Hospital Newcastle, NSW
Mr John Didlick	Policy Analyst	Hepatitis Australia Woden ACT
Dr David Baker	General Practitioner	East Sydney Doctors Darlinghurst, NSW
Olivia Dawson	Project Manager	ASHM
Sonja Hill	Senior Project Officer	ASHM

With thanks to the following reviewers from the Australasian Hepatology Association:

Name	Role	Affiliation
Brooke Andersen	Hepatology Clinical Nurse Consultant	Children's Hospital Westmead Sydney, NSW
Dr Suzanne Sheppard-Law	Senior Lecturer, School of Nursing & Midwifery	University of Technology Sydney, NSW
Charlton Noble	Senior Statewide Paediatric Hepatology & Liver Transplant Coordinator	Queensland Children's Hospital South Brisbane, QLD

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