Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

und

Schriftliche Beteiligung der wissenschaftlich-medizinischen Fachgesellschaften und der Arzneimittelkommission der deutschen Ärzteschaft (AkdÄ) zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

Vorgang: 2025-B-197 Glecaprevir/Pibrentasvir

Stand: September 2025

I. Zweckmäßige Vergleichstherapie: Kriterien gemäß 5. Kapitel § 6 VerfO G-BA

Glecaprevir/Pibrentasvir
[akute Hepatitis C]

Kriterien gemäß 5. Kapitel § 6 VerfO	
Sofern als Vergleichstherapie eine Arzneimittelanwendung in Betracht kommt, muss das Arzneimittel grundsätzlich eine Zulassung für das Anwendungsgebiet haben.	Es sind keine Arzneimittel im Anwendungsgebiet der akuten Hepatitis-C-Infektion zugelassen. Für Arzneimittel zur Behandlung der chronischen Hepatitis-C-Infektion siehe Übersicht „II. Zugelassene Arzneimittel im Anwendungsgebiet“.
Sofern als Vergleichstherapie eine nicht-medikamentöse Behandlung in Betracht kommt, muss diese im Rahmen der GKV erbringbar sein.	nicht angezeigt
Beschlüsse/Bewertungen/Empfehlungen des Gemeinsamen Bundesausschusses zu im Anwendungsgebiet zugelassenen Arzneimitteln/nicht-medikamentösen Behandlungen	Beschlüsse über die Nutzenbewertung gemäß § 35a SGB V zu Wirkstoffen mit Zulassung für die Behandlung der chronischen Hepatitis-C-Infektion: - Elbasvir/Grazoprevir: Beschlüsse vom 15.06.2017 und 05.05.2022 - Glecaprevir/Pibrentasvir: Beschlüsse vom 01.02.2018, 17.10.2019 und 16.12.2021 - Ledipasvir/Sofosbuvir: Beschlüsse vom 21.05.2015, 15.02.2018, 21.01.2021 - Sofosbuvir: Beschlüsse vom 17.07.2014, 05.04.2018 und 21.01.2021 - Sofosbuvir/Velpatasvir: Beschlüsse vom 05.01.2017, 01.04.2021 und 04.08.2022 - Sofosbuvir/Velpatasvir/Voxilaprevir: Beschlüsse vom 15.02.2018 und 07.04.2022
Die Vergleichstherapie soll nach dem allgemein anerkannten Stand der medizinischen Erkenntnisse zur zweckmäßigen Therapie im Anwendungsgebiet gehören.	Siehe systematische Literaturrecherche

II. Zugelassene Arzneimittel im Anwendungsgebiet

Wirkstoff **ATC-Code** **Handelsname**	**Anwendungsgebiet** (Text aus Fachinformation)
Zu bewertendes Arzneimittel:	
Glecaprevir/ Pibrentasvir J05AP57 Maviret	Geplantes Anwendungsgebiet laut Beratungsanforderung: Bei Erwachsenen und Kinder ab 3 Jahren zur Behandlung der **akuten** Hepatitis-C-Virus (HCV)-Infektion angewendet.
Es sind keine Arzneimittel im Anwendungsgebiet der akuten Hepatitis-C-Infektion zugelassen.	
Arzneimittel zur Behandlung der chronischen Hepatitis C:	
Ribavirin J05AP01 Ribavirin-ratiopharm	Ribavirin-ratiopharm in Kombination mit anderen Arzneimitteln ist bestimmt zur Behandlung der chronischen Hepatitis C (CHC) bei vorbehandelten Erwachsenen. (Stand: 01/2025)
Sofosbuvir J05AP08 Sovaldi	Sovaldi wird in Kombination mit anderen Arzneimitteln zur Behandlung der chronischen Hepatitis C (CHC) bei Erwachsenen und bei Kindern und Jugendlichen ab einem Alter von 3 Jahren angewendet (siehe Abschnitte 4.2, 4.4 und 5.1). Zur spezifischen Aktivität gegen die verschiedenen Genotypen des Hepatitis-C-Virus (HCV) siehe Abschnitte 4.4 und 5.1. (Stand: 05/2022)
Ledipasvir/ Sofosbuvir J05AP51 Harvoni	Harvoni wird bei Erwachsenen, Kindern und Jugendlichen ab einem Alter von 3 Jahren zur Behandlung der chronischen Hepatitis C (CHC) angewendet (siehe Abschnitte 4.2, 4.4 und 5.1). Zur spezifischen Aktivität gegen die verschiedenen Genotypen des Hepatitis-C-Virus (HCV) siehe Abschnitte 4.4 und 5.1. (Stand: 11/2022)
Elbasvir/ Grazoprevir J05AP54 Zepatier	Zepatier wird zur Behandlung der chronischen Hepatitis C (CHC) bei Erwachsenen, Jugendlichen und Kindern ab einem Alter von 12 Jahren und einem Körpergewicht von mindestens 30 kg angewendet (siehe Abschnitte 4.2, 4.4 und 5.1). Zur Hepatitis-C-Virus (HCV)-Genotyp-spezifischen Aktivität, siehe Abschnitte 4.4 und 5.1. (Stand 06/2022)

II. Zugelassene Arzneimittel im Anwendungsgebiet	
Sofosbuvir/ Velpatasvir J05AP55 Epclusa	Epclusa wird zur Behandlung der chronischen Hepatitis C-Virusinfektion (HCV) bei Patienten ab einem Alter von 3 Jahren angewendet (Stand: 08/2023)
Sofosbuvir/ Velpatasvir/ Voxilaprevir J05AP56 Vosevi	Vosevi wird zur Behandlung der chronischen Hepatitis C-Virusinfektion (HCV) bei Patienten ab einem Alter von 12 Jahren und mit einem Körpergewicht von mindestens 30 kg angewendet. (Stand: 08/2023)
Peginterferon alfa-2a L03AB11 Pegasys	<u>Chronische Hepatitis C</u> *Erwachsene Patienten* Pegasys ist in Kombination mit anderen Arzneimitteln für die Behandlung der chronischen Hepatitis C (CHC) bei Patienten mit kompensierter Lebererkrankung indiziert (siehe Abschnitte 4.2, 4.4 und 5.1). Zur spezifischen Aktivität gegen die verschiedenen Genotypen des Hepatitis-C-Virus (HCV), siehe Abschnitte 4.2 und 5.1. *Kinder und Jugendliche ab 5 Jahren* Pegasys ist in Kombination mit Ribavirin zur Behandlung von Kindern und Jugendlichen ab 5 Jahren mit bisher noch nicht behandelter CHC, die Serum-HCV-RNA-positiv sind, indiziert. Bei der Entscheidung, die Behandlung im Kindesalter zu beginnen, ist es wichtig zu beachten, dass die Kombinationstherapie zu Wachstumsverzögerungen führen kann. Die Reversibilität einer Wachstumshemmung ist ungewiss. Die Entscheidung für oder gegen eine Behandlung sollte von Fall zu Fall getroffen werden (siehe Abschnitt 4.4). (Stand: 08/2024)

Quellen: AMIce-Datenbank, Fachinformationen

Gemeinsamer Bundesausschuss

Abteilung Fachberatung Medizin

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie

Vorgang: 2025-B-197 (Beratung nach § 35a SGB V) Glecaprevir/Pibrentasvir

Auftrag von:	Abt. AM
Bearbeitet von:	Abt. FB Med
Datum:	21. August 2025

Inhaltsverzeichnis

Abkürzungsverzeichnis

AASLD	American Association for the Study of Liver Diseases
AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
DAA	Direct-acting antiviral
ECRI	Emergency Care Research Institute
FDA	United States Food and Drug Administration
G-BA	Gemeinsamer Bundesausschuss
GIN	Guidelines International Network
GoR	Grade of Recommendations
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
HR	Hazard Ratio
IDSA	Infectious Diseases Society of America
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
KI	Konfidenzintervall
LMICs	Low- and middle-income countries
LoE	Level of Evidence
NICE	National Institute for Health and Care Excellence
OR	Odds Ratio
PK	Pharmacokinetic
QALY	Quality-adjusted life-year
RR	Relatives Risiko
SIGN	Scottish Intercollegiate Guidelines Network
SVR	Sustained virological response
TRIP	Turn Research into Practice Database
WHO	World Health Organization

1 Indikation

Erwachsenen und bei Kindern im Alter von 3 Jahren und älter zur Behandlung der akuten und chronischen Hepatitis-C-Virus (HCV)- Infektion angewendet.

Hinweis zur Synopse: „Informationen hinsichtlich nicht zugelassener Therapieoptionen sind über die vollumfängliche Darstellung der Leitlinienempfehlungen dargestellt“.

2 Systematische Recherche

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen und evidenzbasierten systematischen Leitlinien zur Indikation Hepatitis-C-Virus (HCV)- Infektion durchgeführt und nach PRISMA-S dokumentiert [A]. Die Recherchestrategie wurde vor der Ausführung anhand der PRESS-Checkliste begutachtet [B]. Es erfolgte eine Datenbankrecherche ohne Sprachrestriktion in: The Cochrane Library (Cochrane Database of Systematic Reviews), PubMed. Die Recherche nach grauer Literatur umfasste eine gezielte, iterative Handsuche auf den Internetseiten von Leitlinienorganisationen. Ergänzend wurde eine freie Internetsuche (*https://www.google.com/*) unter Verwendung des privaten Modus, nach aktuellen deutsch- und englischsprachigen Leitlinien durchgeführt.

Der Suchzeitraum der systematischen Literaturrecherche wurde auf die letzten fünf Jahre eingeschränkt und die Recherchen am 22.07.2025 abgeschlossen. Die detaillierte Darstellung der Recherchestrategie inkl. verwendeter Suchfilter sowie eine Auflistung durchsuchter Leitlinienorganisationen ist am Ende der Synopse aufgeführt. Mit Hilfe von EndNote wurden Dubletten identifiziert und entfernt. Die Recherchen ergaben insgesamt 1058 Referenzen.

In einem zweistufigen Screening wurden die Ergebnisse der Literaturrecherche bewertet. Im ersten Screening wurden auf Basis von Titel und Abstract nach Population, Intervention, Komparator und Publikationstyp nicht relevante Publikationen ausgeschlossen. Dabei wurde für systematische Reviews, inkl. Meta-Analysen, ein Publikationszeitraum von 2 Jahren und für Leitlinien von 5 Jahren betrachtet. Zudem wurde eine Sprachrestriktion auf deutsche und englische Referenzen vorgenommen. Im zweiten Screening wurden die im ersten Screening eingeschlossenen Publikationen als Volltexte gesichtet und auf ihre Relevanz und methodische Qualität geprüft. Dafür wurden dieselben Kriterien wie im ersten Screening sowie Kriterien zur methodischen Qualität der Evidenzquellen verwendet. Basierend darauf, wurden insgesamt 4 Referenzen eingeschlossen. Es erfolgt eine synoptische Darstellung wesentlicher Inhalte der identifizierten Referenzen.

3 Ergebnisse

3.1 Cochrane Reviews

Es wurden keine Cochrane Reviews identifiziert.

3.2 Systematische Reviews

Es wurden keine Systematic Reviews identifiziert.

3.3 Leitlinien

Information zur dt. S3 Leitlinie

Die dt. S3-LL *„Prophylaxe, Diagnostik und Therapie der Hepatitis-C-Virus(HCV)-Infektion“* befindet sich aktuell in Überarbeitung und wurde seit ≥ 5 Jahren nicht aktualisiert. Die Fertigstellung ist für den 30.12.2025 geplant.

American Association for the Study of the Liver (AASLD), Infectious Diseases Society of America (IDSA), 2023 [1,2].

HCV Guidance: Recommendations for testing, managing, and treating hepatitis C

Zielsetzung/Fragestellung

The goal of the guidance is to provide up-to-date recommendations to healthcare practitioners on the optimal screening, management, and treatment for persons with HCV infection in the United States, considering the best available evidence. The guidance is updated regularly as new data, information, and tools and treatments become available.

Methodik

Grundlage der Leitlinie

Last Updated: Dec 19, 2023

- Repräsentatives Gremium: trifft teilweise zu (Patientenvertretung unklar)
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt: trifft zu
- Systematische Suche, Auswahl und Bewertung der Evidenz: trifft teilweise zu
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt: unklar
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt: trifft zu
- Regelmäßige Überprüfung der Aktualität gesichert: trifft zu

Recherche/Suchzeitraum:

- Pubmed, Scopus, EMBASE, and Web of Science databases
- Published in English from 2010 to the present

LoE/GoR

- 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.

Adapted from the American College of Cardiology and the American Heart Association Practice Guidelines (AHA, 2011); (Shiffman, 2003).

HCV in Children

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.	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

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.

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.

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).

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.

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.

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

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.	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 have been replicated in the pediatric population. Clinical trial data evaluating DAA regimens in children and adolescents have allowed expanded 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 any genotype of HCV.

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

Recommended regimens listed by pangenotypic, evidence level and alphabetically for

Treatment-Naive or Interferon-Experienced Children and Adolescents Without Cirrhosis or With Compensated Cirrhosis[a]

RECOMMENDED	DURATION	RATING
Combination of glecaprevir/pibrentasvir (weight-based dosing; see Table 1) for children aged ≥ 3 with any genotype[b]	8 weeks	I, B
Combination of sofosbuvir/velpatasvir (weight-based dosing; see Table 2) for children ≥3 of age with any genotype	12 weeks	I, B
Combination of ledipasvir/sofosbuvir (weight-based dosing; see Table 3) for children aged ≥3 years with genotype 1, 4, 5, or 6	12 weeks	I, B

[a] Child-Pugh A
[b] A longer duration of therapy (ie, 16 weeks) may be needed for genotype 3 interferon-experienced patients.

Recommended regimens listed by pangenotypic, evidence level and alphabetically for

DAA-Experienced Children and Adolescents, Without Cirrhosis or With Compensated Cirrhosis[a]

RECOMMENDED	DURATION	RATING
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: Combination of glecaprevir/pibrentasvir (weight-based dosing; see Table 1) 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: Combination of glecaprevir/pibrentasvir (weight-based dosing; see	16 weeks	I, C

Recommended regimens listed by pangenotypic, evidence level and alphabetically for **DAA-Experienced Children and Adolescents, Without Cirrhosis or With Compensated Cirrhosis[a]**		
Table 1) 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]		
Genotype 1- 6: Combination of glecaprevir/pibrentasvir (weight-based dosing; see Table 1) 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- 6: Combination of glecaprevir/pibrentasvir (weight-based dosing; see Table 1) 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
Genotypes 1-6: Combination of sofosbuvir/velpatasvir (weight-based dosing; see Table 2) 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	12 weeks	I, C
Genotypes 1-6: Combination of sofosbuvir/velpatasvir (weight-based dosing; see Table 2) with weight-based ribavirin (see Table 4) with prior exposure to an interferon-based regimen (± ribavirin) and/or sofosbuvir but no exposure to NS3/4A or NS5A protease inhibitors, with decompensated cirrhosis	12 weeks	I, C
Genotype 4, 5, or 6: Combination of ledipasvir/sofosbuvir (weight-based dosing; see Table 3) 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]	12 weeks	I, C
Genotype 1: Combination of ledipasvir/sofosbuvir (weight-based dosing; see Table 3) for children and adolescents aged ≥3 years with prior exposure to an interferon (± ribavirin) plus an HCV protease inhibitor regimen, without cirrhosis	12 weeks	I, C
Genotype 1: Combination of ledipasvir/sofosbuvir (weight-based dosing; see Table 3) for children and adolescents aged ≥3 years with prior exposure to an interferon (± ribavirin) plus an HCV protease inhibitor regimen, with compensated cirrhosis[a]	24 weeks	I, C
[a] Child-Pugh A		

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).

Part 2 of the DORA trial examined the pharmacokinetics, safety and efficacy of glecaprevir/pibrentasvir among children aged 3 to <12 years with HCV of any genotype who were treatment naive or interferon/ribavirin experienced. Although the trial was designed to include children with compensated cirrhosis, none of the participants had cirrhosis at enrollment. The majority (98%; 78/80) of the children who received glecaprevir/pibrentasvir were treatment naive; a single participant was HIV/HCV coinfected. The overall SVR12 with the optimal drug dosages/ratios was 96%. Of the 2 nonresponders, 1 child discontinued treatment after only 1 dose because of palatability and the other after 4 days due to a drug-

related rash. No clinically significant laboratory abnormalities or liver-related toxicities were observed (Jonas, 2021). This regimen was approved for use in children 3 to < 12 years of age in 2021.

Given its pangenotypic activity, safety, and efficacy record in adult patients, glecaprevir/pibrentasvir is recommended as a first choice for pediatric and 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.

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 and for children 3 to < 6 years of age in June 2021. Given its pangenotypic activity, safety, and efficacy, sofosbuvir/velpatasvir is recommended as a first choice for HCV treatment in children and adolescents. Due to reports from experience among adults, coadministration of sofosbuvir/velpatasvir with amiodarone is not recommended due to the risk for symptomatic bradycardia.

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.

Sofosbuvir Plus Ribavirin

In September 2019, the FDA approved weight-based sofosbuvir plus ribavirin (see Table 4) 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). This regimen is no longer favored because pangenotypic ribavirin-free treatments are now available for children as young as 3 years of age.

Referenzen aus Leitlinien

Alter MJ, Kruszon-Moran D, Nainan OV, et al. The prevalence of hepatitis C virus infection in the United States, 1988 through 1994. N Engl J Med. 1999;341(8):556-562.
Aniszewska M, Kowalik-Mikolajewska B, Pokorska-Spiewak M, Marczynska M. Anti-HCV testing as a basic standard of monitoring HCV mother-to-child infection: advantages and disadvantages of the method. Przegl Epidemiol. 2012;66:341-345.
Asselah T, Kowdley KV, Zadeikis N, et al. Efficacy of glecaprevir/pibrentasvir for 8 or 12 weeks in patients with hepatitis C virus genotype 2, 4, 5, or 6 infection without cirrhosis. Clin Gastroenterol Hepatol. 2018;16(3):417-426.
Asselah T, Kowdley KV, Zadeikis N, et al. Efficacy of glecaprevir/pibrentasvir for 8 or 12 weeks in patients with hepatitis C virus genotype 2, 4, 5, or 6 infection without cirrhosis. Clin Gastroenterol Hepatol. 2018;16(3):417-426.
Balistreri WF, Murray KF, Rosenthal P, et al. The safety and effectiveness of ledipasvir-sofosbuvir in adolescents 12-17 years old with hepatitis C virus genotype 1 infection. Hepatology. 2017;66(2):371-378.
Behairy B-S, Sira MM, Zalata KR, Salama el-SE, Abd-Allah MA. Transient elastography compared to liver biopsy and morphometry for predicting fibrosis in pediatric chronic liver disease: Does etiology matter?. World J Gastroenterol. 2016;22(16):4238-4249.
Benova L, Mohamoud YA, Calvert C, Abu-Raddad LJ. Vertical transmission of hepatitis C virus: systematic review and meta-analysis. Clin Infect Dis. 2014;59(6):765-773.
Bortolotti F, Verucchi G, Camma C, et al. Long-term course of chronic hepatitis C in children: from viral clearance to end-stage liver disease. Gastroenterology. 2008;134:1900-1907.
Brown RS, Buti M, Rodrigues L, et al. Efficacy and safety of 8-week glecaprevir/pibrentasvir in treatment-naive patients with chronic hepatitis c virus genotype 1, 2, 3, 4, 5, or 6 infection and compensated cirrhosis: EXPEDITION-8 complete results [abstract LP9]. Presented at Liver Meeting, 2019; November 8-12. 2019.
Casiraghi MAntonietta, De Paschale M, Romanò L, et al. Long-term outcome (35 years) of hepatitis C after acquisition of infection through mini transfusions of blood given at birth. Hepatology. 2004;39(1):90-96.
Cottrell E, Chou R, Wasson N, Rahman B, Guise J-M. Reducing risk for mother-to-infant transmission of hepatitis C virus: a systematic review for the U.S. Preventive Services Task Force. Ann Intern Med. 2013;158(2):109-113.
Cua IH, Hui JM, Kench JG, George J. Genotype-specific interactions of insulin resistance, steatosis, and fibrosis in chronic hepatitis C. Hepatology. 2008;48:723-731.
Delotte J, Barjoan E, Berrébi A, et al. Obstetric management does not influence vertical transmission of HCV infection: results of the ALHICE group study. J Matern Fetal Neonatal Med. 2014;27(7):664-670.
England K, Pembrey L, Tovo PA, Newell ML. Excluding hepatitis C virus (HCV) infection by serology in young infants of HCV-infected mothers. Acta Paediatr. 2005;94:444-450.
European paediatric hepatitis C virus network. A significant sex--but not elective cesarean section--effect on mother-to-child transmission of hepatitis C virus infection. J Infect Dis. 2005;192(11):1872-1879.
Farmand S, Wirth S, Loffler H. Spontaneous clearance of hepatitis C virus in vertically infected children. Eur J Pediatr. 2012;171:253-258.
Forns X, Lee SS, Valdes J, et al. Glecaprevir plus pibrentasvir for chronic hepatitis C virus genotype 1, 2, 4, 5, or 6 infection in adults with compensated cirrhosis (EXPEDITION-1): a single-arm, open-label, multicentre phase 3 trial. Lancet Infect Dis. 2017;17(10):1062-1068.
Garazzino S, Calitri C, Versace A, et al. Natural history of vertically acquired HCV infection and associated autoimmune phenomena. Eur J Pediatr. 2014;173:1025-1031.
Geng X-X, Huang R-G, Lin J-M, Jiang N, Yang X-X. Transient elastography in clinical detection of liver cirrhosis: a systematic review and meta-analysis. Saudi J Gastroenterol. 2016;22(4):294-303.
Gonzalez-Peralta RP, Langham MR, Andres JM, et al. Hepatocellular carcinoma in 2 young adolescents with chronic hepatitis C. J Pediatr Gastroenterol Nutr. 2009;48(5):630-635.
Goodman ZD, Makhlouf HR, Liu L, et al. Pathology of chronic hepatitis C in children: liver biopsy findings in the Peds-C trial. Hepatology. 2008;47(3):836-843.
Gowda C, Smith S, Crim L, Moyer K, Sanchez PJ, . Nucleic Acid Testing for Diagnosis of Perinatally Acquired Hepatitis C Virus Infection in Early Infancy. Clin Infect Dis. 2021;73(9):e3340-e3346. doi:10.1093/cid/ciaa949.
Gower E, Estes C, Blach S, Razavi-Shearer K, Razavi H. Global epidemiology and genotype distribution of the hepatitis C virus infection. J Hepatol. 2014;61(1 Suppl):S45-S57.
Greenway E, Haines A, Ling SC, et al. Cost-utility analysis of treatment of chronic paediatric hepatitis C with new direct-acting antivirals [abstract 1619]. The Liver Meeting 2019. 2019.
Honegger J, Crim L, Gowda C, Sanchez PJ. Polymerase chain reaction (PCR) for detection of vertically-acquired hepatitis C virus (HCV) infection in early infancy [abstract 2215]. ID Week. 2018.
Indolfi G, Easterbrook P, Dusheiko GM, et al. Hepatitis C virus infection in children and adolescents. Lancet Gastroenterol Hepatol. 2019;4:477-487.

Jacobson IM, Gordon SC, Kowdley KV, et al. Sofosbuvir for hepatitis C genotype 2 or 3 in patients without treatment options. N Engl J Med. 2013;368:1867-1877.
Jhaveri R. Diagnosis and management of hepatitis C virus-infected children. Pediatr Infect Dis J. 2011;30(11):983-985.
Jonas MM, Squires RH, Rhee S, et al. Pharmacokinetics, safety, and efficacy of glecaprevir/pibrentasvir in adolescents with chronic hepatitis C virus: part 1 of the DORA study. Hepatology. 2019:[Epub ahead of print]. doi:10.1002/hep.30840.
Jonas MM, Romero R, Sokal EM, et al. Safety and efficacy of sofosbuvir/velpatasvir in pediatric patients 6 to <18 years old with chronic hepatitis C infection [abstract 748]. The Liver Meeting. 2019.
Jonas MM, Lon HK, Rhee S, et al. Pharmacokinetics of glecaprevir/pibrentasvir in children with chronic HCV infection: interim analysis of part 2 of the DORA study [abstract 1551]. The Liver Meeting. Boston. 2019.
Jonas MM, Rhee S, Kelly DA, et al. Pharmacokinetics, safety, and efficacy of glecaprevir/pibrentasvir in children with chronic hepatitis C virus: part 2 of the DORA study. Hepatology. 2021;74(1):19-27. doi:10.1002/hep.31841.
Kukla M, Piotrowski D, Waluga M, Hartleb M. Insulin resistance and its consequences in chronic hepatitis C. Clin Exp Hepatol. 2015;1(1):17-29.
Lawitz E, Mangia A, Wyles D, et al. Sofosbuvir for previously untreated chronic hepatitis C infection. N Engl J Med. 2013;368:1878-1887.
Lee CK, Perez-Atayde AR, Mitchell PD, Raza R, Afdhal NH, Jonas MM. Serum biomarkers and transient elastography as predictors of advanced liver fibrosis in a United States cohort: the Boston Children's Hospital experience. J Pediatr. 2013;163(4):1058-1064.e2.
Mack CL, Gonzalez-Peralta RP, Gupta N, et al. NASPGHAN practice guidelines: diagnosis and management of hepatitis C infection in infants, children, and adolescents. J Pediatr Gastroenterol Nutr. 2012;54(6):838-855.
Marrero JA, Kulik LM, Sirlin CB. Diagnosis, staging, and management of hepatocellular carcinoma: 2018 practice guidance by the American Association for the Study of Liver Diseases. Hepatology. 2018;68(2):723-750.
Mast EE, Hwang L-Y, Seto DSY, et al. Risk factors for perinatal transmission of hepatitis C virus (HCV) and the natural history of HCV infection acquired in infancy. J Infect Dis. 2005;192(11):1880-1889.
Minola E, Prati D, Suter F, et al. Age at infection affects the long-term outcome of transfusion-associated chronic hepatitis C. Blood. 2002;99(12):4588-4591.
Mizuochi T, Takano T, Yanagi T, et al. Epidemiologic features of 348 children with hepatitis C virus infection over a 30-year period: a nationwide survey in Japan. J Gastroenterol. 2018;53:419-426.
Moucari R, Asselah T, Cazals-Hatem D, et al. Insulin resistance in chronic hepatitis C: association with genotypes 1 and 4, serum HCV RNA level, and liver fibrosis. Gastroenterology. 2008;134:416-423.
Murray KF, Balistreri WF, Bansal S, et al. Safety and efficacy of ledipasvir-sofosbuvir with or without ribavirin for chronic hepatitis C in children ages 6-11. Hepatology. 2018;68:2158-2166.
Nguyen J, Barritt AS, Jhaveri R. Cost effectiveness of early treatment with direct-acting antiviral therapy in adolescent patients with hepatitis C infection. J Pediatr. 2019;(207):90-96. doi:10.1016/j.jpeds.2018.12.012.
Nielsen J, Christensen VB, Borgwardt L, Rasmussen A, Ostrup O, Kjaer MS. Prognostic molecular markers in pediatric liver disease - Are there any?. Biochim Biophys Acta Mol Basis Dis. 2019;(1865):577-586.
Petta S, Camma C, DiMarco V, et al. Hepatic steatosis and insulin resistance are associated with severe fibrosis in patients with chronic hepatitis caused by HBV or HCV infection. Liver Int. 2011;31:507-515.
Pokorska-Spiewak M, Kowalik-Mikolajewska B, Aniszewska M, Pluta M, Marczynska M. Clinical usefulness of new noninvasive serum biomarkers for the assessment of liver fibrosis and steatosis in children with chronic hepatitis C. Clin Exp Hepatol. 2017;3:198-202.
Puoti M, Foster GR, Wang S, et al. High SVR12 with 8-week and 12-week glecaprevir/pibrentasvir therapy: An integrated analysis of HCV genotype 1-6 patients without cirrhosis. J Hepatol. 2018;69(2):293-300.
Resti M, Jara P, Hierro L, et al. Clinical features and progression of perinatally acquired hepatitis C virus infection. J Med Virol. 2003;70:373-377.
Rosenthal P, Schwarz KB, Gonzalez-Peralta RP, et al. Sofosbuvir and ribavirin therapy for children aged 3 to <12 years with hepatitis C virus genotype 2 or 3 infection. Hepatology. 2020;71(1):31-43.
Schmidt AJ, Falcato L, Zahno B, et al. Prevalence of hepatitis C in a Swiss sample of men who have sex with men: whom to screen for HCV infection?. BMC Public Health. 2014;14(1):3.
Schwarz KB, Rosenthal P, Murray KF, et al. Ledipasvir-sofosbuvir for 12 weeks in children 3 to <6 years old with chronic hepatitis C. Hepatology. 2019;DOI 10.1002/hep.30830 [Epub ahead of print]. doi:10.1002/hep.30830.
Shebl FM, El-Kamary SS, Saleh D'aA, et al. Prospective cohort study of mother-to-infant infection and clearance of hepatitis C in rural Egyptian villages. Abdel-Hamid M, Mikhail N, Allam A, et al., eds. J Med Virol. 2009;81(6):1024-1031.
Sulkowski MS, Naggie S, Lalezari J, et al. Sofosbuvir and ribavirin for hepatitis C in patients with HIV coinfection. Fessel WJ, Mounzer K, Shuhart M, et al., eds. JAMA. 2014;312(4):353-361.

Tieu HV, Laeyendecker O, Nandi V, et al. Prevalence and mapping of hepatitis C infections among men who have sex with men in New York City. PLoS One. 2018:13:e0200269.
Vaux S, Chevaliez S, Saboni L, et al. Prevalence of hepatitis C infection, screening and associated factors among men who have sex with men attending gay venues: a cross-sectional survey (PREVAGAY), France, 2015. BMC Infect Dis. 2019;19:315.
Wirth S, Rosenthal P, Gonzalez-Peralta RP, et al. Sofosbuvir and ribavirin in adolescents 12-17 years old with hepatitis C virus genotype 2 or 3 infection. Hepatology. 2017;66(4):1102-1110.
Wyles D, Poordad F, Wang S, et al. Glecaprevir/pibrentasvir for hepatitis C virus genotype 3 patients with cirrhosis and/or prior treatment experience: a partially randomized phase 3 clinical trial: viral hepatitis. Hepatology. 2018;67(2):514-523.
Yeung LT, To T, King SM, Roberts EA. Spontaneous clearance of childhood hepatitis C virus infection. J Viral Hepat. 2007;14:797-805.
Zeuzem S, Dusheiko GM, Salupere R, et al. Sofosbuvir and ribavirin in HCV genotypes 2 and 3. N Engl J Med. 2014;370:1993-2001.
Zeuzem S, Foster GR, Wang S, et al. Glecaprevir-pibrentasvir for 8 or 12 weeks in HCV genotype 1 or 3 Infection. N Engl J Med. 2018;378(4):354-369. doi:10.1056/NEJMoa1702417.

Management of Acute HCV Infection

Acute hepatitis C infection is most often asymptomatic and frequently develops into chronic infection. Case reports of acute hepatitis C have increased in the US since 2010 and have most often been associated with parenteral exposures to blood or body fluids (CDC, 2019). Although HCV infection is primarily associated with injection drug use, certain behaviors (eg, unprotected [without a condom] receptive anal intercourse)—primarily among men who have sex with men—are risk factors for transmission (Lockart, 2019); (Price, 2019). The syndemic of opioid use disorder and HCV and HIV transmission contributes to the burden of disease in certain populations (Butt, 2020).

<u>Pharmacologic Prophylaxis</u>

Pharmacologic Prophylaxis Not Recommended	
NOT RECOMMENDED	RATING
Pre-exposure or post-exposure prophylaxis with antiviral therapy is not recommended.	III, C

There are no data on the efficacy or cost-effectiveness of antiviral therapy for pre-exposure or post-exposure prophylaxis of HCV infection.

Medical Management and Monitoring of Acute HCV Infection

Recommendations for Medical Management and Monitoring of Acute HCV Infection	
RECOMMENDED	RATING
After the initial diagnosis of acute HCV with viremia (defined as quantifiable RNA), HCV treatment should be initiated without awaiting spontaneous resolution.	I, B
Counseling is recommended for patients with acute HCV infection to avoid hepatotoxic insults, including hepatotoxic drugs (eg, acetaminophen) and alcohol consumption, and to reduce the risk of HCV transmission to others.	I, C
Referral to an addiction medicine specialist is recommended for patients with acute HCV infection related to substance use.	I, B

Patients with acute HCV infection should be treated upon initial diagnosis without awaiting spontaneous resolution, using a “test and treat” strategy and according to the simplified approach, if eligible. Real-world data have demonstrated a reduction in HCV viremia prevalence and incidence with unrestricted access to HCV therapy (Boerekamps, 2018). In addition, mathematical modeling suggests that DAA treatment scale-up, especially among those at highest risk of transmission, can reduce HCV incidence and prevalence (Martin, 2013); (Martin, 2016). Moreover, delay introduced by waiting for spontaneous clearance may be associated with loss to follow up.

Individuals with acute HCV should be counseled to reduce behaviors that could result in virus transmission, such as sharing injection equipment and engaging in high-risk sexual practices. Because the risk of transmission of other bloodborne, sexually transmitted infections (eg, HIV and HBV) is higher in the acute infection phase, some experts counsel patients with acute HCV to consider using barrier precautions, even in a stable monogamous relationship (see Testing and Linkage to Care). For individuals with acute HCV infection who have a history of recent injection drug use, referral to harm reduction services and an addiction medicine specialist is recommended when appropriate (Litwin, 2009); (Strathdee, 2005).

Patients with acute hepatitis C are often asymptomatic or have nonspecific symptoms (eg, fatigue, anorexia, mild or moderate abdominal pain, low-grade fever, nausea, and/or vomiting) that frequently are not recognized as being associated with acute HCV infection. A small proportion (<25%) of patients with acute HCV develop jaundice. Patients diagnosed with acute HCV should initially be monitored with hepatic panels (ALT, aspartate aminotransferase [AST], bilirubin, and international normalized ratio [INR] in the setting of an increasing bilirubin level) at 2- to 4-week intervals (Blackard, 2008). With treatment, a rapid improvement of laboratory parameters is expected.

There is no need to alter concomitant medications that are metabolized by hepatic enzymes unless there is concern for developing acute liver failure (eg, increasing bilirubin level and INR). Acetaminophen and alcohol consumption should be avoided during acute HCV infection (Proeschold-Bell, 2012); (Dieperink, 2010); (Whitlock, 2004).

Hospitalization is rarely indicated unless nausea and vomiting are severe. Although acute liver failure is very rare (<1%), it represents a serious and life-threatening complication of acute HCV infection. Patients with an INR >1.5 and those who exhibit any signs of acute liver failure (eg, hepatic encephalopathy) should be referred to a liver transplant center

immediately. Use of HCV antiviral regimens in acute liver failure should be managed by a clinician experienced in HCV treatment, ideally in consultation with a liver transplant specialist.

HCV infection spontaneously clears in 20% to 50% of patients (Kamal, 2008). Clearance of acute HCV infection occurs within 6 months of the estimated time of infection (median, 16.5 weeks) in at least 2/3 of patients who spontaneously clear HCV. Only 11% of those who remain viremic at 6 months will spontaneously clear the infection at a later time (Grebely, 2014). Patients who have spontaneously cleared should not be treated with antiviral therapy. However, they should be counseled about the possibility of reinfection and tested routinely for this development if risk behaviors are ongoing (see Testing and Linkage to Care). Of note, transient suppression of viremia can occur in those with acute HCV infection, even among those who progress to chronic infection. Thus, a single undetectable HCV RNA test result is insufficient to declare spontaneous clearance (see Testing and Linkage to Care) (Villano, 1999); (Mosley, 2008).

Predictors of spontaneous clearance include jaundice, elevated ALT level, hepatitis B virus surface antigen (HBsAg) positivity, female sex, younger age, genotype 1 infection, and host genetic polymorphisms, most notably those near the IL28B gene (Kamal, 2008); (Mosley, 2008).

Antiviral Therapy

Recommended Regimens for Patients With Acute HCV Infection	
RECOMMENDED	RATING
Owing to high efficacy and safety, the same regimens that are recommended for chronic HCV infection are recommended for acute infection.	IIa, C

A number of studies have evaluated DAA treatment of acute HCV infection. Small single-arm, uncontrolled studies have evaluated 6 or 8 weeks of ledipasvir/sofosbuvir. One such study demonstrated 100% SVR with 8 weeks of ledipasvir/sofosbuvir among 27 men with acute HCV and HIV-coinfection (Naggie, 2019). Investigators conducting another study evaluated 6 weeks of ledipasvir/sofosbuvir in a similar cohort (25/26 with HIV coinfection). Among participants with genotype 1 infection, 79% (15/19) achieved SVR12; 71% (5/7) of those with genotype 4 infection achieved SVR12 with this shortened regimen. Among the 6 individuals whose treatment did not lead to SVR12, there were 3 relapses (all had baseline HCV RNA levels >7 log10 IU/mL). Three participants achieved SVR4 but were lost to follow-up (Rockstroh, 2017b). A phase 2 study followed a similar treatment protocol (ie, 6 weeks of ledipasvir/sofosbuvir) among 20 individuals with genotype 1 HCV monoinfection, all of whom achieved SVR12 (Deterding, 2017).

An open-label, single-arm, multicenter pilot study evaluated the efficacy of 6 weeks of the pangenotypic regimen glecaprevir/pibrentasvir among persons with acute/recent HCV infection (ie, duration of infection <12 months). SVR12 was 90% (27/30); a single virological failure occurred in a man with genotype 1a, HIV coinfection, and a viral load of 7.7 log10 IU/mL. This patient was successfully retreated (Martinello, 2020).

In the only randomized trial to date, investigators compared 6 vs 12 weeks of sofosbuvir/velpatasvir in the international REACT trial of acute/recent infection. The study was stopped early due to inferiority of the shortened (ie, 6 week) arm. In the 6-week arm,

81.7% (76/93) (on ITT) and 89.4% (76/85) (on mITT) of participants achieved SVR with 6 relapses and 8 nonvirologic failures. In the 12-week group, 90.5% (86/95) on ITT and 97.7% (86/88) (on mITT) achieved SVR with no virologic failures (3 participants were lost to follow-up). There were no clear predictors of relapse aside from shorter treatment duration (Matthews, 2021).

To date, there are insufficient data to support a particular regimen or treatment duration outside of a clinical trial. Until more definitive data are available, treatment as described for chronic hepatitis C is recommended (see Initial Treatment of HCV Infection). Pangenotypic regimens are recommended if HCV genotyping is unavailable or if concern of exposure to more than 1 genotype exists. Using the same regimens to treat acute/recent HCV as for chronic HCV infection also simplifies management, as defining acute HCV may be clinically challenging.

Referenzen aus Leitlinien

Blackard JT, Shata MT, Shire NJ, Sherman KE. Acute hepatitis C virus infection: a chronic problem. Hepatology. 2008;47(1):321-331.

Boerekamps A, van den Berk GE, Lauw FN. Declining hepatitis C virus (HCV) incidence in Dutch human immunodeficiency virus-positive men who have sex with men after unrestricted access to HCV therapy. Clin Infect Dis. 2018;66(9):1360-1365. doi:10.1093/cid/cix1007.

Bruneau J, Zang G, Abrahamowicz M, Jutras-Aswad D, Daniel M, Roy E. Sustained drug use changes after hepatitis C screening and counseling among recently infected persons who inject drugs: a longitudinal study. Clin Infect Dis. 2014;58(6):755-761.

Butt ZA, Wong S, Rossi C, et al. Concurrent hepatitis C and B virus and human immunodeficiency virus infections are associated with higher mortality risk illustrating the impact of syndemics on health outcomes. Open Forum Infect Dis. 2020;7(9):ofaa347.

US Centers for Disease Control and Prevention. Viral hepatitis surveillance—United States, 2017. Atlanta, GA: US Department of Health and Human Services, CDC; 2019. Available at: https://www.cdc.gov/hepatitis/statistics/2017surveillance/index.htm. Accessed May 26, 2021.

Chamot E, Hirschel B, Wintsch J, et al. Loss of antibodies against hepatitis C virus in HIV-seropositive intravenous drug users. AIDS. 1990;4(12):1275-1277.

Cox AL, Netski DM, Mosbruger T, et al. Prospective evaluation of community-acquired acute-phase hepatitis C virus infection. Clin Infect Dis. 2005;40(7):951-958.

Deterding K, Spinner CD, Schott E, et al. Ledipasvir plus sofosbuvir fixed-dose combination for 6 weeks in patients with acute hepatitis C virus genotype 1 monoinfection (HepNet Acute HCV IV): an open-label, single-arm, phase 2 study. Lancet Infect Dis. 2017;17(2):215-222. doi:10.1016/S1473-3099(16)30408-X.

Dieperink E, Ho SB, Heit S, Durfee JM, Thuras P, Willenbring ML. Significant reductions in drinking following brief alcohol treatment provided in a hepatitis C clinic. Psychosomatics. 2010;51(2):149-156.

Goldenberg SM, Montaner J, Braschel M, Socias E, Guillemi S, Shannon K. Dual sexual and drug-related predictors of hepatitis C incidence among sex workers in a Canadian setting: gaps and opportunities for scale-up of hepatitis C virus prevention, treatment, and care. Int J Infect Dis. 2017;55:31-37.

Grebely J, Page K, Sacks-Davis R, et al. The effects of female sex, viral genotype, and IL28B genotype on spontaneous clearance of acute hepatitis C virus infection. Hepatology. 2014;59(1):109-120.

Kamal SM. Acute hepatitis C: a systematic review. Am J Gastroenterol. 2008;103(5):1283-1297.

Kim AY, Nagami EH, Birch CE, Bowen MJ, Lauer GM, McGovern BH. A simple strategy to identify acute hepatitis C virus infection among newly incarcerated injection drug users. Hepatology. 2013;57(3):944-952.

Kushner T, Serper M, Kaplan DE. Delta hepatitis within the Veterans Affairs medical system in the United States: Prevalence, risk factors, and outcomes. J Hepatol. 2015;63(3):586-592.

Litwin AH, Harris KA, Nahvi S, et al. Successful treatment of chronic hepatitis C with pegylated interferon in combination with ribavirin in a methadone maintenance treatment program. J Subst Abuse Treat. 2009;37(1):32-40.

Lockart I, Matthews GV, Danta M. Sexually transmitted hepatitis C infection: the evolving epidemic in HIV-positive and HIV-negative MSM. Curr Opin Infect Dis. 2019;32(1):31-37.

Martin NK, Hickman M, Hutchinson SJ, Goldberg DJ, Vickerman P. Combination interventions to prevent HCV transmission among people who inject drugs: modeling the impact of antiviral treatment, needle and syringe programs, and opiate substitution therapy. Clin Infect Dis. 2013;57(Suppl 2):S39-S45.

Martin NK, Thornton A, Hickman M, et al. Can hepatitis C virus (HCV) direct-acting antiviral treatment as prevention reverse the HCV epidemic among men who have sex with men in the United Kingdom? Epidemiological and modeling insights. Clin Infect Dis. 2016;62(9):1072-1080.

Martinello M, Orkin C, Cooke G, et al. Short-duration pan-genotypic therapy with glecaprevir/pibrentasvir for 6 weeks among people with recent hepatitis C viral infection. Hepatology. 2020;72(1):7-18.
Matthews GV, Bhagani S, Van der Valk M, et al. Sofosbuvir/velpatasvir for 12 vs 6 weeks for the treatment of recently acquired hepatitis C infection. J Hepatol. 2021;S0168-8278(21):00336-6.
McGovern BH, Birch CE, Bowen MJ, et al. Improving the diagnosis of acute hepatitis C virus infection with expanded viral load criteria. Clin Infect Dis. 2009;49(7):1051-1060.
Mosley JW, Operskalski EA, Tobler LH, et al. The course of hepatitis C viraemia in transfusion recipients prior to availability of antiviral therapy. J Viral Hepat. 2008;15(2):120-128.
Naggie S, Fierer DS, Hughes M, et al. 100% SVR with 8 weeks of ledipasvir/sofosbuvir in HIV-infected men with acute HCV infection: results from the SWIFT-C trial [abstract]. Hepatology. 2017;66(Suppl.):196.
Naggie S, Fierer DS, Hughes MD, et al. Ledipasvir/sofosbuvir for 8 weeks to treat acute hepatitis C virus infections in men with human immunodeficiency virus infections: sofosbuvir-containing regimens without interferon for treatment of acute HCV in HIV-1 infected individuals. Clin Infect Dis. 2019;69(3):514-522.
Price JC, McKinney JE, Crouch PC, et al. Sexually acquired hepatitis C infection in HIV-uninfected men who have sex with men using preexposure prophylaxis against HIV. J Infect Dis. 2019;219(9):1373-1376.
Proeschold-Bell RJ, Patkar AA, Naggie S, et al. An integrated alcohol abuse and medical treatment model for patients with hepatitis C. Dig Dis Sci. 2012;57(4):1083-1091.
Rockstroh JK, Bhagani S, Hyland RH, et al. Ledipasvir-sofosbuvir for 6 weeks to treat acute hepatitis C virus genotype 1 or 4 infection in patients with HIV coinfection: an open-label, single-arm trial. Lancet Gastroenterol Hepatol. 2017;2(5):347-353. doi:10.1016/S2468-1253(17)30003-1.
Smith BD, Jewett A, Burt RD, Zibbell JE, Yartel AK, DiNenno E. "To share or not to share?" Serosorting by hepatitis C status in the sharing of drug injection equipment among NHBS-IDU2 participants. J Infect Dis. 2013;208(12):1934-1942.
Strathdee SA, Latka M, Campbell J, et al. Factors associated with interest in initiating treatment for hepatitis C virus (HCV) infection among young HCV-infected injection drug users. O'Driscoll PT, Golub ET, Kapadia F, et al., eds. Clin Infect Dis. 2005;40(Suppl 5):S304-S312.
Todesco E, Day N, Amiel C, et al. High clustering of acute HCV infections and high rate of associated STIs among Parisian HIV-positive male patients. Int J Antimicrob Agents. 2019;53(5):678-681.
Villano SA, Vlahov D, Nelson KE, Cohn S, Thomas DL. Persistence of viremia and the importance of long-term follow-up after acute hepatitis C infection. Hepatology. 1999;29(3):908-914.
Whitlock EP, Polen MR, Green CA, Orleans T, Klein J. Behavioral counseling interventions in primary care to reduce risky/harmful alcohol use by adults: a summary of the evidence for the US Preventive Services Task Force. Ann Intern Med. 2004;140(7):557-568.

When and in Whom to Initiate HCV Therapy

Goal of Treatment	
RECOMMENDED	RATING ⓘ
The goal of treatment of HCV-infected persons is to reduce all-cause mortality and liver-related health adverse consequences, including end-stage liver disease and hepatocellular carcinoma, by the achievement of virologic cure as evidenced by a sustained virologic response.	I, A

Recommendation for When and in Whom to Initiate Treatment	
RECOMMENDED	RATING ⓘ
Treatment is recommended for all patients with acute or chronic HCV infection, except those with a short life expectancy that cannot be remediated by HCV therapy, liver transplantation, or another directed therapy. Patients with a short life expectancy owing to liver disease should be managed in consultation with an expert.	I, A

Pretreatment Assessment

Recommendation for Pretreatment Assessment	
RECOMMENDED	RATING
Evaluation for advanced fibrosis using noninvasive markers and/or elastography, and rarely liver biopsy, is recommended for all persons with HCV infection to facilitate decision making regarding HCV treatment strategy and determine the need for initiating additional measures for the management of cirrhosis (eg, hepatocellular carcinoma screening) (see HCV Testing and Linkage to Care).	I, A

Initial Treatment of Adults with HCV Infection

Initial treatment of HCV infection includes patients with chronic hepatitis C who have not been previously treated with interferon, peginterferon, ribavirin, or any HCV direct-acting antiviral (DAA) agent, whether investigational, or US Food and Drug Administration (FDA) approved.

Simplification of the treatment regimen may expand the number of healthcare professionals who prescribe antiviral therapy and increase the number of persons treated. This would align with the National Academies of Science, Engineering, and Medicine strategy to reduce cases of chronic HCV infection by 90% by 2030 (NAS, 2017).

- Simplified Pangenotypic HCV Treatment for Treatment-Naive Adults Without Cirrhosis
- Simplified Pangenotypic HCV Treatment Algorithm for Treatment-Naive Adults With Compensated Cirrhosis

The level of evidence available to inform the best regimen for each patient and the strength of the recommendation vary and are rated accordingly (see Methods Table 2). In addition, specific recommendations are given when treatment differs for a particular group (eg, those infected with different genotypes). Recommended regimens are those that are favored for most patients in a given group, based on optimal efficacy, favorable tolerability and toxicity profiles, and treatment duration. Alternative regimens are those that are effective but, relative to recommended regimens, have potential disadvantages, limitations for use in certain patient populations, or less supporting data than recommended regimens. In certain situations, an alternative regimen may be an optimal regimen for an individual patient or clinical setting. Specific considerations for pediatric patients and persons with HIV/HCV coinfection, decompensated cirrhosis (moderate or severe hepatic impairment; Child-Turcotte- Pugh [CTP] class B or C), HCV infection post liver transplant, and severe renal impairment, end-stage renal disease (ESRD), or post kidney transplant are addressed in other sections of the guidance.

Recommended and alternative regimens are listed by pan-genotypic activity and in order of level of evidence. When several regimens are at the same recommendation level, they are listed in alphabetical order. Regimen choice should be determined based on patient-specific data, including drug-drug interactions. Patients receiving antiviral therapy require careful pretreatment assessment for comorbidities that may influence treatment response or regimen selection. All patients should have access to an HCV care provider during treatment, although preset clinic visits and/or blood tests depend on the treatment regimen and may not be required for all regimens/patients. Patients receiving ribavirin require additional monitoring for anemia during treatment (see Monitoring section).

Simplified HCV Treatment* for Treatment-Naive Adults Without Cirrhosis

Who Is *NOT* Eligible for Simplified Treatment (Without Cirrhosis)

Patients who have any of the following characteristics:

- Prior hepatitis C treatment
- Cirrhosis (see simplified treatment for treatment-naive adults with compensated cirrhosis)
- HBsAg positive
- Current pregnancy
- Known or suspected hepatocellular carcinoma
- Prior liver transplantation

(see HCV guidance for treatment recommendations for these patients)

Who Is Eligible for Simplified Treatment

Adults with chronic hepatitis C (any genotype) who do not have cirrhosis and have not previously received hepatitis C treatment

Recommended Regimens*

- Glecaprevir (300 mg) / pibrentasvir (120 mg) to be taken with food for a duration of 8 weeks
- Sofosbuvir (400 mg) / velpatasvir (100 mg) for a duration of 12 weeks

Simplified HCV Treatment Algorithm for Treatment-Naive Adults With Compensated Cirrhosis

Who Is *NOT* Eligible for Simplified Treatment (With Cirrhosis)

Patients who have any of the following characteristics:

- Current or prior episode of decompensated cirrhosis, defined as Child-Turcotte-Pugh (CTP) score ≥7 (ascites, hepatic encephalopathy, total bilirubin >2.0 mg/dL, albumin ≤3.5 g/dL, or INR ≥1.7)
- Prior hepatitis C treatment
- End-stage renal disease (ie, eGFR <30 mL/min/m^2) (see Patients with Renal Impairment section)
- HBsAg positive
- Current pregnancy
- Known or suspected hepatocellular carcinoma
- Prior liver transplantation

(see HCV guidance for treatment recommendations for these patients)

Who Is Eligible for Simplified Treatment

Adults with chronic hepatitis C (any genotype) who have compensated cirrhosis (Child-Pugh A) and have not previously received hepatitis C treatment

Liver biopsy is not required. For the purpose of this guidance, a patient is presumed to have cirrhosis if they have a FIB-4 score >3.25 **or** any of the following findings from a previously performed test.

- Transient elastography indicating cirrhosis (eg, FibroScan stiffness >12.5 kPa)
- Noninvasive serologic tests above proprietary cutoffs indicating cirrhosis (eg, FibroSure, Enhanced Liver Fibrosis Test, etc)
- Clinical evidence of cirrhosis (eg, liver nodularity and/or splenomegaly on imaging, platelet count <150,000/mm^3, etc)
- Prior liver biopsy showing cirrhosis

Recommended Regimens*

- **Genotype 1-6**:
  Glecaprevir (300 mg) / pibrentasvir (120 mg) to be taken with food for a duration of 8 weeks

- **Genotype 1, 2, 4, 5, or 6**
  Sofosbuvir (400 mg) / velpatasvir (100 mg) for a duration of 12 weeks
  NOTE: Patients with genotype 3 require baseline NS5A resistance-associated substitution (RAS) testing. Those without Y93H can be treated with 12 weeks of sofosbuvir/velpatasvir. If Y93H is present, see HCV guidance for treatment recommendations.

Treatment-Naive Genotype 1

Three highly potent DAA combination regimens are recommended for patients with genotype 1 infection, although there are differences in the recommended regimens based on the HCV subtype, the presence or absence of baseline NS5A resistance-associated substitutions (RASs), and the presence or absence of compensated cirrhosis.

With certain regimens, patients with genotype 1a may have higher virologic failure rates than those with genotype 1b. Genotype 1 infection that cannot be subtyped should be treated as genotype 1a infection.

Approximately 10% to 15% of genotype 1-infected patients without prior exposure to NS5A inhibitors have detectable NS5A RASs prior to treatment. The clinical impact of NS5A RASs varies across regimens and baseline patient characteristics. In patients with genotype 1a infection, the presence of baseline NS5A RASs that cause a large reduction in the activity of NS5A inhibitors (>5 fold) adversely impacts response to some NS5A inhibitor-containing regimens (Zeuzem, 2017); (Jacobson, 2015b). These RASs are found by population sequencing in roughly 5% to 10% of patients and relevant RASs vary by DAA regimen. Given that baseline NS5A RASs are one of the strongest pretreatment predictors of therapeutic response with certain regimens in those with genotype 1a infection, testing for these RASs prior to deciding on a therapeutic course is recommended in select situations (Zeuzem, 2015c). In clinical settings where RAS testing is unavailable, regimens for which the presence of specific RAS(s) factor into treatment selection should be avoided. For further guidance, please see the HCV Resistance Primer section.

Compared to interferon-based therapy, DAAs are associated with a higher rate of drug-drug interactions with concomitant medications. Thus, attention to drug interactions is an important treatment consideration (see Drug Interactions table). The product prescribing information and other resources (eg, http://www.hep-druginteractions.org) should be referenced regularly to ensure safety when prescribing DAA regimens. Important interactions with commonly used medications (eg, antacids, lipid-lowering drugs, anti-epileptics, antiretrovirals, etc) exist for all the regimens discussed.

Treatment-Naive Genotype 1a Without Cirrhosis

Recommended and alternative regimens listed by pangenotypic, evidence level and alphabetically for:

Treatment-Naive Genotype 1a Patients Without Cirrhosis

RECOMMENDED	DURATION	RATING
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg)[a]	8 weeks	I, A
Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg)	12 weeks	I, A
Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) for patients who are HIV-uninfected and whose HCV RNA level is <6 million IU/mL	8 weeks	I, B
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)	12 weeks	I, A
ALTERNATIVE	DURATION	RATING
Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg)	12 weeks	I, A

[a] Dosing is 3 coformulated tablets (glecaprevir [100 mg]/pibrentasvir [40 mg]) taken once daily. Please refer to the prescribing information.

Treatment-Naive Genotype 1a With Compensated Cirrhosis

Recommended and alternative regimens listed by pangenotypic, evidence level and alphabetically for: **Treatment-Naive Genotype 1a Patients With Compensated Cirrhosis**[a]		
RECOMMENDED	DURATION	RATING
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)	12 weeks	I, A
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg)[b]	8 weeks	I, B
Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg)	12 weeks	I, A
ALTERNATIVE	DURATION	RATING
Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg)	12 weeks	I, A

[a] For decompensated cirrhosis, please refer to the appropriate section.
[b] Dosing is 3 coformulated tablets (glecaprevir [100 mg]/pibrentasvir [40 mg]) taken once daily. Please refer to the prescribing information.

Treatment-Naive Genotype 1b Without Cirrhosis

Recommended and alternative regimens listed by pangenotypic, evidence level and alphabetically for: **Treatment-Naive Patients Genotype 1b Without Cirrhosis**		
RECOMMENDED	DURATION	RATING
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg)[a]	8 weeks	I, A
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)	12 weeks	I, A
Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg)	12 weeks[b]	I, A
Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg)	12 weeks	I, A
Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) for patients who are HIV-uninfected and whose HCV RNA level is <6 million IU/mL	8 weeks[c]	I, B

[a] Dosing is 3 coformulated tablets (glecaprevir [100 mg]/pibrentasvir [40 mg]) taken once daily. Please refer to the prescribing information.
[b] For HIV/HCV coinfected patients, a treatment duration of 12 weeks is recommended.
[c] An 8-week regimen can be considered in those with genotype 1b infection and mild fibrosis (see text for details).

Treatment-Naive Genotype 1b With Compensated Cirrhosis

Recommended and alternative regimens listed by pangenotypic, evidence level and alphabetically for: **Treatment-Naive Genotype 1b Patients With Compensated Cirrhosis**[a]		
RECOMMENDED	DURATION	RATING
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)	12 weeks	I, A
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg)[b]	8 weeks	I, B
Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg)	12 weeks	I, A
Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg)	12 weeks	I, A

[a] For decompensated cirrhosis, please refer to the appropriate section.
[b] Dosing is 3 coformulated tablets (glecaprevir [100 mg]/pibrentasvir [40 mg]) taken once daily. Please refer to the prescribing information.

Treatment-Naive Genotype 2

Treatment-Naive Genotype 2 Without Cirrhosis

Recommended and alternative regimens listed by pangenotypic, evidence level and alphabetically for: **Treatment-Naive Genotype 2 Patients Without Cirrhosis**		
RECOMMENDED	DURATION	RATING
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg)[a]	8 weeks	I, A
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)	12 weeks	I, A
[a] Dosing is 3 coformulated tablets (glecaprevir [100 mg]/pibrentasvir [40 mg]) taken once daily. Please refer to the prescribing information.		

Treatment-Naive Genotype 2 With Compensated Cirrhosis

Recommended and alternative regimens listed by pangenotypic, evidence level and alphabetically for: **Treatment-Naive Genotype 2 Patients With Compensated Cirrhosis[a]**		
RECOMMENDED	DURATION	RATING
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)	12 weeks	I, A
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg)[b]	8 weeks	I, B
[a] For decompensated cirrhosis, please refer to the appropriate section. [b] Dosing is 3 coformulated tablets (glecaprevir [100 mg]/pibrentasvir [40 mg]) taken once daily. Please refer to the prescribing information.		

Treatment-Naive Genotype 3

Treatment-Naive Genotype 3 Without Cirrhosis

Recommended and alternative regimens listed by pangenotypic, evidence level and alphabetically for: **Treatment-Naive Genotype 3 Patients Without Cirrhosis**		
RECOMMENDED	DURATION	RATING
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg)[a]	8 weeks	I, A
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)	12 weeks	I, A
[a] Dosing is 3 coformulated tablets (glecaprevir [100 mg]/pibrentasvir [40 mg]) taken once daily. Please refer to the prescribing information.		

Treatment-Naive Genotype 3 With Compensated Cirrhosis

Recommended and alternative regimens listed by pangenotypic, evidence level and alphabetically for: **Treatment-Naive Genotype 3 Patients With Compensated Cirrhosis**[a]		
RECOMMENDED	DURATION	RATING
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) for patients without baseline NS5A RAS Y93H	12 weeks	I, A
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg)[b]	8 weeks	I, B
ALTERNATIVE	DURATION	RATING
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) with weight-based ribavirin for patients with baseline NS5A RAS Y93H	12 weeks	IIa, A
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)/voxilaprevir (100 mg) for patients with baseline NS5A RAS Y93H	12 weeks	IIa, B

[a] For decompensated cirrhosis, please refer to the appropriate section.
[b] Dosing is 3 coformulated tablets (glecaprevir [100 mg]/pibrentasvir [40 mg]) taken once daily. Please refer to the prescribing information.

Treatment-Naive Genotype 4

Treatment-Naive Genotype 4 Without Cirrhosis

Recommended and alternative regimens listed by pangenotypic, evidence level and alphabetically for: **Treatment-Naive Genotype 4 Patients Without Cirrhosis**		
RECOMMENDED	DURATION	RATING
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg)[a]	8 weeks	I, A
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)	12 weeks	I, A
Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg)	12 weeks	I, A
Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg)[b]	12 weeks	I, A

[a] Dosing is 3 coformulated tablets (glecaprevir [100 mg]/pibrentasvir [40 mg]) taken once daily. Please refer to the prescribing information.
[b] An 8-week regimen can be considered in patients with favorable baseline characteristics (ie, no cirrhosis, HCV RNA <6 million IU/mL, and absence of genotype 4r).

Treatment-Naive Genotype 4 With Compensated Cirrhosis

Recommended and alternative regimens listed by pangenotypic, evidence level and alphabetically for: **Treatment-Naive Genotype 4 Patients With Compensated Cirrhosis[a]**		
RECOMMENDED	DURATION	RATING
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)	12 weeks	I, A
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg)[b]	8 weeks[c]	I, B
Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg)	12 weeks	IIa, B
Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg)	12 weeks	IIa, B

[a] For decompensated cirrhosis, please refer to the appropriate section.
[b] Dosing is 3 coformulated tablets (glecaprevir [100 mg]/pibrentasvir [40 mg]) taken once daily. Please refer to the prescribing information.
[c] For HIV/HCV-coinfected patients, a treatment duration of 12 weeks is recommended.

Treatment-Naive Genotype 5 or 6

Recommended and alternative regimens listed by pangenotypic, evidence level and alphabetically for: **Treatment-Naive Genotype 5 or 6 Patients With and Without Compensated Cirrhosis[a]**		
RECOMMENDED	DURATION	RATING
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg)[b]	8 weeks	I, A[c]
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)	12 weeks	I, B
Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg)[d]	12 weeks	IIa, B

[a] For decompensated cirrhosis, please refer to the appropriate section.
[b] Dosing is 3 coformulated tablets (glecaprevir [100 mg]/pibrentasvir [40 mg]) taken once daily. Please refer to the prescribing information.
[c] For compensated cirrhosis, rating is I, B.
[d] Not recommended for genotype 6e if subtype is known.

Retreatment of Persons in Whom Prior Therapy Failed

Sofosbuvir-Based and Elbasvir/Grazoprevir Treatment Failures

Recommended and alternative regimens listed by evidence level and alphabetically for: **Sofosbuvir-Based Treatment Failures, With or Without Compensated Cirrhosis**[a]		
RECOMMENDED	DURATION	RATING
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)/voxilaprevir (100 mg)[b]	12 weeks	I, A
ALTERNATIVE	DURATION	RATING
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) except for NS3/4 protease inhibitor inclusive combination DAA regimen failures[c] • **Not** recommended for genotype 3 infection with sofosbuvir/NS5A inhibitor experience.	16 weeks	I, A
[a] For decompensated cirrhosis, please refer to the appropriate section. [b] Genotype 3: Add weight-based ribavirin if cirrhosis is present and there are no contraindications. [c] This regimen is not recommended for patients with prior exposure to an NS5A inhibitor plus NS3/4 PI regimens (e.g., elbasvir/grazoprevir).		

Glecaprevir/Pibrentasvir Treatment Failures

Recommended regimens listed by evidence level and alphabetically for: **Glecaprevir/Pibrentasvir Treatment Failures (All Genotypes), With or Without Compensated Cirrhosis**[a]		
RECOMMENDED	DURATION	RATING
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) plus daily sofosbuvir (400 mg) and weight-based ribavirin	16 weeks	IIa, B
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)/voxilaprevir (100 mg)	12 weeks	IIa, B
For patients with compensated cirrhosis, addition of weight-based ribavirin is recommended.	12 weeks	IIa, C
[a] For decompensated cirrhosis, please refer to the appropriate section.		

Multiple DAA Treatment Failures (All Genotypes), Including Sofosbuvir/Velpatasvir/Voxilaprevir or Sofosbuvir Plus Glecaprevir/Pibrentasvir

Recommended regimens listed by evidence level and alphabetically for:

Sofosbuvir/Velpatasvir/Voxilaprevir Treatment Failures, With or Without Compensated Cirrhosis[a]

RECOMMENDED	DURATION	RATING
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) plus daily sofosbuvir (400 mg) and weight-based ribavirin	16 weeks[b]	IIa, B
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)/voxilaprevir (100 mg) plus weight-based ribavirin	24 weeks	IIa, B

[a] For decompensated cirrhosis, please refer to the appropriate section.
[b] Extension of treatment to 24 weeks should be considered in extremely difficult cases (e.g., genotype 3 with cirrhosis) or failure following sofosbuvir plus glecaprevir/pibrentasvir.

World Health Organization et al., 2022 [4].

World Health Organization (WHO)

Updated recommendations on treatment of adolescents and children with chronic HCV infection, and HCV simplified service delivery and diagnostics

Zielsetzung/Fragestellung

The objective of these guidelines is to provide updated evidence-based recommendations on the priority HCV-related topics from the 2018 WHO Guidelines for the care and treatment of persons diagnosed with chronic hepatitis C infection and the 2017 WHO Guidelines on hepatitis B and C testing. These priority areas are:

- direct-acting antiviral (DAA) treatment of adolescents and children ages ≥3 years of age
- simplified HCV service delivery (decentralization, integration and task sharing)
- HCV diagnostics – use of point-of-care (POC) HCV ribonucleic acid (RNA) assays and reflex
- HCV RNA testing.

Methodik

Grundlage der Leitlinie

- Repräsentatives Gremium: trifft zu
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt: trifft zu
- Systematische Suche, Auswahl und Bewertung der Evidenz: trifft zu
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt: trifft zu
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt: trifft zu
- Regelmäßige Überprüfung der Aktualität gesichert: unklar

Recherche/Suchzeitraum:

Five systematic external reviews and meta-analyses of the primary literature were commissioned externally to address the research questions and outcomes important to

patients. Outcomes were ranked by the Guidelines Development Group based on their importance to the patient population.

These included: ·

- the efficacy and safety of direct-acting antivirals in children and adolescents with chronic HCV infection; [3]
- decentralization, integration and task-sharing in hepatitis C virus infection testing and treatment; ·
- impact of HCV PoC HCV RNA viral load testing on uptake of testing and treatment and turnaround times and diagnostic accuracy of PoC HCV RNA viral load assays; · determining the threshold/lower limit of detection required for HCV RNA viral load assays for test of cure following treatment with direct-acting antiviral (DAA) based treatment regimens; ·
- laboratory-based and clinic-based HCV viral load reflex testing following an initial positive HCV antibody test result.

LoE

TABLE 3.1 GRADE categories of the certainty of evidence

Certainty of evidence	Rationale
High	We are very confident that the true effect lies close to the estimate of effect.
Moderate	We are moderately confident of the estimate of effect. The true effect is likely to be close to the estimate of effect, but it could be substantially different.
Low	Our confidence in the estimate of effect is limited. The true effect may be substantially different from the estimate of effect.
Very low	We have very little confidence in the estimate of effect. Any estimate of effect is very uncertain.
Simeprevir	Pibrentasvir

GoR

The GRADE system classifies the strength of a recommendation in two ways: “strong” and “conditional” (65).

- A **strong recommendation** is one for which the Guidelines Development Group was confident that the desirable effects of adhering to the recommendation outweigh the undesirable effects.
- A **conditional recommendation** is one for which the Guidelines Development Group concluded that the desirable effects of adhering to the recommendation probably outweigh the undesirable effects but the Guidelines Development Group is not confident about these trade-offs. The implications of a conditional recommendation are that, although most people or settings would adopt the recommendation, some would not or would do so only under certain conditions. The reasons for making a conditional recommendation include the absence of high-certainty evidence, imprecision in outcome estimates, uncertainty regarding how individuals value the outcomes, small benefits relative to harms, and benefits that may not be worth the costs (including the costs of implementing the recommendation).

Sonstige methodische Hinweise

- These guidelines also include updates to existing chapters without any new recommendations, such as inclusion of new manufacturers' protocols on use of dried blood spots (DBS) for serology and HCV RNA viral load testing and new data to inform limit of detection for HCV RNA viral load assays as a test of cure. Overall, this guideline update is consistent with the modular approach to updates adopted since 2020 in response to emerging evidence on hepatitis B and C virus infections. The first modular update, on hepatitis C self-testing, was launched in July 2021 (5). This guidelines update constitutes the second modular update on hepatitis C testing and treatment. A modular update on hepatitis B testing and treatment is planned for 2022 based on existing hepatitis B treatment (6) and testing guidelines (4). In 2023, all updates will be compiled along with existing recommendations into a single consolidated guidelines on prevention, testing, care and treatment of hepatitis B and C, containing all relevant guidance.

CHAPTER 4. TREATMENT FOR ADULTS, ADOLESCENTS AND CHILDREN (≥3 YEARS)

4.1 New recommendations: treatment of adolescents (12–17 years), older children (6–11 years) and younger children (3–5 years); and existing 2018 recommendations for adults (1)

Whom to treat?

New recommendations (for adolescents and children) and existing recommendations for adults (1)

We recommend treatment using pangenotypic DAA regimens for the treatment of all adults, adolescents and children ages 3 years and above with chronic hepatitis C infection, regardless of stage of disease:

Adults (≥18 years)[1]: *strong recommendations; moderate certainty of evidence*

Adolescents (12–17 years)[2]: *strong recommendation; moderate/low certainty of evidence*

Older children (6–11 years): *strong recommendation; moderate/very low certainty of evidence*

Younger children (3–5 years): *conditional recommendation; very low certainty of evidence*

[1] Existing 2018 recommendation from Guidelines for the care and treatment of persons diagnosed with chronic hepatitis C infection *(1)*. Pangenotypic is defined as SVR rate of >85% across all six major HCV genotypes.

[2] For consistency, we use the same age groupings as those used in the trials for regulatory submissions.

What DAA regimens to use?

New recommendations (for adolescents and children) and existing recommendations for adults *(1)*

We recommend the use of the following pangenotypic DAA regimens is recommended in adults (18 years and above), adolescents (12–17 years), older children (6–11 years) (*all strong recommendations*) and younger children (3–5 years) (*conditional recommendation*):

- **SOF/DCV**[1] for 12 weeks:[2] *certainty of evidence: high (adults), high (adolescents and older children); very low (younger children)*
- **SOF/VEL** for 12 weeks: *certainty of evidence: high (adults), low (adolescents and older children); very low (younger children)*
- **G/P** for eight weeks: *certainty of evidence: high (adults), moderate (adolescents and older children); very low (younger children).*

1 Most widely used regimen in adults due to availability of quality-assured, low-cost generics.

2 In those without cirrhosis. Treatment for 24 weeks in those who are treatment-experienced or with compensated cirrhosis.

TABLE 4.1. Duration of treatment

Age groups	Pangenotypic DAA regimens			Non-pangenotypic DAA regimen (in settings with minimal GT3 infection)[2]
	Sofosbuvir/ daclatasvir[1]	Sofosbuvir/ velpatasvir[2]	Glecaprevir/ pibrentasvir	Sofosbuvir/ ledipasvir2
Adults (18 years and above)	12 weeks	12 weeks	8 weeks	12 weeks
Adolescents (12–17 years)	12 weeks	12 weeks	8 weeks	12 weeks
Older children (6–11 years)	12 weeks	12 weeks	8 weeks	12 weeks
Younger children (3–5 years)	12 weeks	12 weeks	8 weeks	12 weeks

1 In those without cirrhosis. Treatment for 24 weeks is recommended in those who are treatment experienced or with compensated cirrhosis. May be considered in settings where genotype 3 is known to be highly prevalent (>10%).

2 For use in those with genotype 1, 4, 5, or 6 infection.

TABLE 4.2. Dosing by weight bands

Pangenotypic DAA regimens			Non-pangenotypic DAA regimens (in settings with minimal GT3 infection)[1]
Sofosbuvir/ daclatasvir[2]	Sofosbuvir/ velpatasvir	Glecaprevir/ pibrentasvir[3]	Sofosbuvir/ ledipasvir
>26 kg 400/60 mg od (film-coated tablets)	>30 kg 400/100 mg od (FDC tablet)	>45 kg 300/120 mg od (FDC tablet or 6 packets of oral pellets)	≥35kg 90/400 mg od (FDC tablet)
14–25 kg 200 mg/30 mg[2] (as single tablets, sofosbuvir preferred as smaller 100 mg tablet)	17–29 kg 200/50 mg od (FDC tablet or granules)	30–<45 kg 250/100 mg od (5 packets of oral pellets) 20–<30 kg 200/80 mg od (4 packets of oral pellets)	17– 35kg 45/200 mg (tablet)
	<17 kg 150/37.5 mg od (coated granules)	<20 kg 150/60mg od (3 packets of oral pellets)	<17 kg 33.75/150 mg (FDC granules packets)

[1] For use in those with genotype 1, 4, 5, or 6 infection or where genotype 3 infection is uncommon. In the SHARED trial, (in adults) a sustained virological response (SVR) with sofosbuvir (400 mg) and ledipasvir (90 mg) was observed in 261 (87%) overall, but in only 56% of those infected with HCV genotype 4r, compared with 93% of those infected with genotype subtypes other than 4r. Realistically, these findings do not support the use of sofosbuvir–ledipasvir as the initial therapy for HCV infection without genotype subtyping in some regions and countries in sub-Saharan Africa.

[2] Dosing based on population pharmacokinetic modelling studies

[3] Available as tablets (FDC) 100/40 mg and oral pellets or granules 50/20 mg, depending on locally approved product information

4.2 Background

Short-course, oral, curative direct-acting antiviral (DAA) regimens have transformed treatment for HCV infection in adults, who bear the greatest burden of morbidity and mortality. This result has been due to high efficacy and minimal side effects with short-course treatment compared with the previous era of interferon-based regimens. Until recently, there had been less attention to addressing HCV in children and adolescents, and no DAA regimens were approved for use in children (67, 68). In 2018 there were an estimated 3.26 million (95%, uncertainty interval 2.07–3.90) children and adolescents ages 0-18 years living with chronic HCV infection (69). The predominant mode of acquisition of HCV infection in children is mother-to-child transmission. Older children and adolescents may become infected via unsafe injections and poor infection prevention and control, especially in LMICs (69, 70). Regardless of age, most children with HCV infection have asymptomatic or minimally symptomatic liver disease, and cirrhosis, hepatocellular carcinoma or extrahepatic manifestations are rare. Yet, recent evidence suggests that those with perinatal exposure developed cirrhosis at an earlier age (71). HCV infection may also decrease the general health and quality of life of adolescents (72, 73). Therefore, early diagnosis and treatment in children is key to preventing long-term morbidity (74). Prior to regulatory approval of DAAs for use in children, the standard of care of adolescents and children infected with HCV was dual therapy with pegylated-interferon alpha and ribavirin for 24 weeks for genotypes 2 and 3, and 48 weeks for genotypes 1 and 4 (75-83). This combination resulted in an SVR rate of around 52% for HCV genotypes 1 and 4 and 89% for HCV genotypes 2 and 3 (75, 76, 78, 80), but it was associated with significant side-effects. At the time of the 2018 WHO HCV guidelines, none of the recommended pangenotypic DAAs for adults (sofosbuvir/ daclatasvir, sofosbuvir/velpatasvir, glecaprevir/pibrentasvir) had been approved for use in either adolescents or children. Therefore, WHO recommended use of two non-pangenotypic DAA regimens (sofosbuvir/ledipasvir and sofosbuvir/ribavirin) that had received regulatory approval from the FDA and the EMA for use in adolescents (≥12 years) (84, 85) but advised deferral of treatment in those under than 12 years of age until DAA regimens became available for these younger age groups (73, 86).

Since 2018, the high rate of HCV viral clearance observed in adults with the various pangenotypic DAA regimens has been replicated among adolescents and children. This led to approvals by the key regulatory agencies, the FDA and the EMA. Among adolescents, the pangenotypic regimens, glecaprevir/pibrentasvir, sofosbuvir/velpatasvir and sofosbuvir/velpatasvir/voxilaprevir, were approved in 2020 and 2021. Among children ages three years and older, sofosbuvir/ledipasvir was approved in 2019, followed by glecaprevir/pibrentasvir and sofosbuvir/velpatasvir in 2021. Although the sofosbuvir/daclatasvir regimen is the most widely available and lowest cost pangenotypic DAA regimen in LMICs, and its safety and efficacy in children and adolescents have been reported in multiple observational studies (87, 88), there is no

regulatory approval for this DAA combination, as the originator companies are no longer collaborating (89). Alignment of WHO-recommended DAA regimens across adults, adolescents and children would simplify procurement, promote access to treatment among children in LMICs and help support global elimination efforts.

4.3 Summary of the evidence for treatment in adolescents and children (Web Annex C)

A WHO-commissioned systematic review and meta-analysis of the efficacy and safety of key DAA regimens was undertaken for adolescents (12‑18 years), older children (6‑11 years) and younger children (3‑5 years) with chronic hepatitis C virus infection, based on the same age groupings used in the trials for regulatory approval. There were 49 studies (three RCTS, 28 non-RCTs and 18 observational studies). Together, they reported treatment experience in 1891 adolescents (35 study arms), 472 older children (13 study arms) and 167 younger children (7 study arms). There were no placebo-controlled RCTs, and findings were based on summary estimates of SVR cure rates by regimen in the three age groups. However, these were considered informative because spontaneous clearance is rare in the absence of treatment. Data on serious adverse events and treatment discontinuations were considered more informative than adverse events alone because of the lack of a comparison group. The majority of participants were non-cirrhotic (1786, 70.6%), treatment-naive (1825, 72.1%), and with non-GT3 infection (1453, 57.4%). Overall, sustained virological response rates 12 weeks after the end of treatment (SVR12) were high (≥95%) in all age groups and for the key pangenotypic DAA regimens as well as for sofosbuvir/ ledipasvir. The rate of any adverse event was higher for children ages 3‑5 years (72%) than for those ages 6‑11 years (53%) or adolescents (50%), but serious adverse events and treatment discontinuations were uncommon (<1%), except in young children (6.6%) because of the poor palatability of the oral formulation of sofosbuvir/velpatasvir in this group. Less than half of the studies (22/49 (44.9%)) reported information on comorbidities. There were 15 persons with cirrhosis across nine studies, 304 persons who were treatment-experienced across 21 studies and 157 persons with GT3 infection across eight studies. There were no studies of sofosbuvir/ daclatasvir in children or adolescents reported from sub-Saharan Africa, where HCV genotype 4 non-a/d subtypes are endemic in some regions, as well as other genotypes (including genotype 1 and 3) that frequently contain resistance-associated substitutions in the NS5A regions. This may contribute to higher rates of treatment failure with sofosbuvir/daclatasvir.

> Virologic response rates after treatment were ≥95% in all age groups and for the key pangenotypic DAA regimens.

All studies but two were classified as at low risk of bias.

4.3.1 Adolescents (12–17 years)

Of the 1891 adolescents included in 35 study arms, 183 received sofosbuvir/daclatasvir (the majority for 12 weeks), 102 sofosbuvir/velpatasvir (12 weeks), 47 glecaprevir/pibrentasvir (44 for eight weeks and three for 16 weeks), and 1686 received sofosbuvir/ledipasvir (12 weeks). All were non-cirrhotic; 1167 (52%) had non-genotype 3 infection, and 274 (14%) patients had treatment experience.

SVR12: Overall, SVR12 was 99% (95% CI: 98‑100) among the 1891 adolescents, with good tolerability and minimal heterogeneity. SVR12 was 99% (96‑100) for sofosbuvir/daclatasvir, 95% (90‑99) for sofosbuvir/velpatasvir, 98% (91‑100) for glecaprevir/pibrentasvir and 99% *(98-100)* for sofosbuvir/ledipasvir.

Adverse events and treatment discontinuations: Of the studies that reported adverse events, 318 (50%) of the adolescents reported at least one adverse event, but only six were considered serious adverse effects. Only 10 adolescents (0.5%) discontinued treatment.

Strength of evidence: high for sofosbuvir/daclatasvir, moderate for glecaprevir/pibrentasvir and sofosbuvir/ledipasvir, and low for sofosbuvir/velpatasvir. Evidence was downgraded mainly for inconsistency and imprecision.

4.3.2. Older children (6–11 years)

Of the 472 older children included in 13 study arms, 73 received sofosbuvir/velpatasvir (12 weeks), 56 received glecaprevir/pibrentasvir (8, 12 or 16 weeks), 34 received sofosbuvir/ daclatasvir (12 weeks) and

178 received sofosbuvir/ledipasvir for 12 weeks. All participants except three were non-cirrhotic; all but seven were treatment-naïve; and the majority were infected with non-genotype 3.

SVR12: Overall, SVR12 was 99% (95% CI: 97–100%) and there was minimal heterogeneity. SVR12 was 100% (94–100) for sofosbuvir/daclatasvir, 93% (86–98) for sofosbuvir/velpatasvir, 96% (90–100) for glecaprevir/pibrentasvir and 100% (97-100) for sofosbuvir/ledipasvir.

Adverse events and treatment discontinuations: Of the studies that reported adverse events, 226 (53%) children reported at least one adverse event, but none was rated as serious. four of 490 children (1%) discontinued treatment, which in three children was due to adverse events (auditory hallucinations, drug-related rash, headache).

Strength of evidence: moderate for sofosbuvir/daclatasvir, glecaprevir/pibrentasvir, and sofosbuvir/ledipasvir; and very low for all other DAA treatment regimens evaluated, due mainly to inconsistency and imprecision.

4.3.3. Younger children (3–5 years)

Of the 167 younger children included in seven study arms, 41 received sofosbuvir/velpatasvir (12 weeks), 25 received glecaprevir/pibrentasvir (8 or 12 weeks), and 56 received other regimens. All except one were non-cirrhotic and treatment-naïve. SVR12: Overall, 95% (95% CI: 89–99) attained SVR12, and there was no evidence of heterogeneity. SVR12 was 83% (70–93) for sofosbuvir/velpatasvir, 92% (77–100) but 96% (80-99) for DORA study Part 2) for glecaprevir/pibrentasvir, and 99% (93–100) for sofosbuvir/ledipasvir. There were no study data for sofosbuvir/daclatasvir. The lower SVR12 in those receiving sofosbuvir/velpatasvir was due to seven discontinuations (not virological failure) because of difficulties in taking the oral medication.

Adverse events and treatment discontinuations: Of the studies that reported adverse events, 92 (72%) reported at least one adverse event; the most common were vomiting (21%), cough (14%) and diarrhoea (9%). Treatment discontinuations were rare, but were higher (6.6%) in the sofosbuvir/velpatasvir arms because of relative lack of palatability of the oral formulation.

Strength of evidence: moderate for sofosbuvir/ledipasvir; very low for all other DAAs (sofosbuvir/velpatasvir, glecaprevir/pibrentasvir). There were no data for sofosbuvir/daclatasvir. There were insufficient studies that reported on outcomes by cirrhosis, genotype and treatment experience. Only three studies reported the HIV co-infection status of participants. There were five HIV co-infected participants, of whom three were treated with glecaprevir/pibrentasvir; all achieved SVR12 (90-92). Overall, the small numbers of HCV-infected children means that subgroup analyses will be limited.

4.3.4 Quality of life assessment

Data from three studies indicate that HCV infection in children has a detrimental effect on quality of life, leading to increased caregiver stress, strain on the family system and poorer health status, including impaired psychosocial and cognitive functioning *(93-95)*. Three other studies explored the impact of DAA treatment on the quality of life of children and adolescents. They showed improvement in health-related quality of life scores after achieving SVR12 *(90, 96, 97)*.

4.3.5 Supporting pharmacokinetic (PK) data for use of 200/30 mg sofosbuvir/daclatasvir in children ages <12 years *(101)*

Sofosbuvir/daclatasvir (400 mg/60 mg) is the pangenotypic DAA regimen of choice for adults and adolescents in many LMICs, as it is highly effective and widely available as low-cost generic formulations. However, there are no direct study data on its efficacy and safety in children ages three to five years. It is recognised that the use of available adult daclatasvir formulations (60 mg and 30 mg) together with approved paediatric doses of sofosbuvir (200 mg and 150 mg) would be an effective way to expand global access to HCV treatment for children. The use of extrapolation to support paediatric drug development is a well-established practice in regulatory approvals *(98)*, whereby efficacy, safety and PK data in young children is extrapolated from adequate studies in adult, adolescents or older children. This applies when the course of the disease or condition and the response to treatment are expected to be similar in children and adults. Modelling and simulation is a critical step in identifying the correct dose, to be confirmed in a targeted PK study. Extrapolation is specifically cited in FDA guidance as appropriate in development of DAAs for children *(67)*. The PK data were used to complement the available clinical data on SVR rates for older children, but they did not change the quality rating. A PK analysis was undertaken to predict

daclatasvir exposure in children less than 12 years of age and weighing 10 to <35 kg, using existing adult 60 mg and 30 mg doses of daclatasvir, and to determine the lowest body weight at which children could be treated using these doses. Daclatasvir concentration data from 17 HCV-infected adolescents receiving sofosbuvir/ daclatasvir (400 mg/60 mg once daily) who participated in a PK study in Egypt were used for model development *(99,100)* . PK parameters were estimated using a population approach. Monte Carlo simulations were run for virtual children weighing 10 to <35 kg receiving 60 or 30 mg once daily, and daclatasvir exposures were compared with ranges seen in adults. Daclatasvir 30 mg once daily was predicted to achieve effective and safe exposures in children 14 to <35 kg and even down to 10 kg *(101)*. Two complementary studies assessed sofosbuvir pharmacokinetics in children relative to adults to establish appropriate dosing in children. One study evaluated PK of sofosbuvir 200 mg and sofosbuvir/ledipasvir 200 mg/45 mg in children ages 6 to <12 years and weighing ≥17 and <45 kg *(86)*. Sofosbuvir and GS-331007 Area under the curve (AUC) and Cmax in children ages 6 to <12 years were within predefined PK equivalence boundaries of 50‑200%. A further open-label study of sofosbuvir/ribavirin in children ages 3‑<12 years used sofosbuvir 200 mg (6‑<12 years), 200 mg (3‑<6 years and ≥17 kg) and 150 mg (3‑<6 years and <17 kg)*(102)*. Overall, exposures were comparable to those observed in adults *(103)*, but Cmax was higher *(104)*. Overall, the data suggest that it would be acceptable to use the existing adult dose of sofosbuvir/ daclatasvir (400 mg/60 mg) in children down at least to 25 kg and a half dose (200 mg/30 mg) for those 14‑25 kg, potentially down even to 10 kg. Two efficacy, safety and PK studies of sofosbuvir/daclatasvir among children <12 years of age are now planned in Egypt and Cambodia to validate the optimal dosing in the intended paediatric population as the basis for regulatory approval and country adoption.

4.4 Rationale for the recommendations

4.4.1. Balance of benefits and harms

Treat all adolescents and children ≥ 3 years with chronic hepatitis C infection

The Guidelines Development Group made a strong recommendation for treatment of all adolescents and children ages 6‑11 years with chronic hepatitis C infection, regardless of stage of disease, based on high/moderate certainty of evidence, and a conditional recommendation for treatment of those ages 3‑5 years, based on moderate/very low certainty of evidence in younger children, for the following reasons:

1. Benefits of earlier treatment in childhood and adolescence include the possibility of achieving a cure before the onset of disease progression, thus preventing HCV-associated liver damage and extrahepatic manifestations. The overall resulting reduction in transmission will reduce the prevalence and incidence in children and adolescents to achieve an HCVfree generation. Although advanced liver disease is uncommon in children and adolescents, liver fibrosis progresses over time and may lead to complications in late adolescence and/ or early adulthood. Other potential reported benefits of early treatment include avoiding stigmatization of infected children and the prevention of transmission to others, particularly among adolescents engaging in high-risk behaviours. It also improves neurocognitive dysfunction that affects school performance and quality of life.

2. Treatment of HCV infected children and adolescents (3–17 years of age) is highly effective and safe, with SVR12 rates ≥95% in all age groups for the key pangenotypic DAA regimens already recommended for adults (sofosbuvir/daclatasvir, glecaprevir/pibrentasvir and sofosbuvir/velpatasvir). This conclusion is based on high, moderate and low certainty of evidence, respectively, for adolescents and older children and very low certainty for all regimens in younger children.

3. Serious adverse events and treatment discontinuations were uncommon. Although the frequency of any adverse event was higher for younger age groups (72% for children ages 3‑5 years, 53% for those ages 6‑11 years and 50% for adolescents), serious adverse events and treatment discontinuations were uncommon. Therefore, the benefit-to-harm ratio is very high in adolescents and older children, but it may be less in younger children, as they experienced more problems with treatment discontinuations due to poor palatability with some regimens and adverse effects.

Treat adolescents ages 12–17 years and older children ages 6–11 years (weighing at least 35 kg) with sofosbuvir/velpatasvir, glecaprevir/pibrentasvir or sofosbuvir/daclatasvir (Web Annex B).

The Guidelines Development Group recommended that all chronically HCV-infected adolescents and older children should be offered treatment with the current FDA- and EMA- approved pangenotypic DAA regimens of sofosbuvir/velpatasvir and glecaprevir/pibrentasvir, as well as sofosbuvir/daclatasvir, previously recommended in adults, based on the following rationale:

1. Both direct evidence from a systematic review and meta-analysis of use of these DAA regimens in 1891 adolescents (12‑18 years of age) from 35 studies and 472 older children (6‑11 years of age) from 13 studies confirmed high efficacy, safety and tolerability, as did indirect evidence from adult treatment studies for all DAA regimens.

2. The PK modelling data suggest that it should be possible to use the existing adult dose of sofosbuvir/daclatasvir (400 mg/60 mg) in children down at least to 25 kg.

3. This new recommendation replaces ribavirin which requires haematological monitoring, with the use of sofosbuvir in adolescents. Also, ribavirin is a teratogenic agent and contraindicated in pregnancy. This is particularly relevant, as adolescents' pregnancies are more likely to be unplanned. 4. Data on treatment in those with cirrhosis remains limited, but recommendations include those with compensated cirrhosis. In those who are treatment-experienced and with compensated cirrhosis, treatment for 24 weeks is recommended.

Treat children ages 3–5 years

The 2018 HCV guidelines recommended that treatment be deferred in young children until they either reach 12 years of age or DAA regimens were approved for those under 12 years of age. This recommendation was based largely on the low frequency of HCV-related liver disease in childhood and the significant side-effects of interferon alpha ‑ some irreversible *(79, 80, 105- 109)* ‑ and overall low efficacy, prolonged treatment duration (6‑12 months), inconvenient administration route (via injection) and high costs. It was recommended that interferon-based regimens should no longer be used for either adolescents or children.

The Guidelines Development Group recognized that the benefits of treatment with DAAs (sofosbuvir/velpatasvir, glecaprevir/pibrentasvir, sofosbuvir/daclatasvir) likely outweigh those of deferral even in those less than six years of age, who are at low risk of advanced liver disease *(110, 111)*. A conditional recommendation was made to initiate DAA treatment in children ages 3‑5 years based on the following rationale:

1. Curative short-course oral pangenotypic DAA regimens (sofosbuvir/velpatasvir, glecaprevir/ pibrentasvir) as well as also sofosbuvir/ledipasvir now have regulatory approval for children down to three years of age.

2. There was high efficacy and no major safety concerns across these regimens ‑ sofosbuvir/ velpatasvir and glecaprevir/pibrentasvir based on direct studies and sofosbuvir/daclatasvir based on extrapolation from studies in adolescent and older children.

3. Overall, the data suggest that it should be possible to use the existing adult dose of sofosbuvir/ daclatasvir (400 mg/60 mg) in children down at least to 25 kg and a half dose (200 mg /30 mg) for those weighing 14‑25 kg, potentially down even to 10 kg.

4. For sofosbuvir/daclatasvir, the modelling exercise based on PK data in adolescents indicated that half of the adult dose (that is, 200 mg/30 mg) could be used for children weighing 14‑25 kg and potentially down even to 10 kg. As noted above, the use of extrapolation to support paediatric drug development is a well-established practice in regulatory approvals *(98,112)*, whereby efficacy, safety and PK data in young children can be extrapolated from adequate studies in adult, adolescents or older children. Extrapolation can be applied when the course of the disease or condition and the response to treatment are expected to be similar in children and adults and matching drug exposure in children to the safe and effective exposure in adults reliably predicts successful treatment. This situation meets all key conditions that support extrapolation of the efficacy observed in adults receiving sofosbuvir/daclatasvir. A PK/efficacy and safety study will be conducted in children to confirm that the proposed dose provides exposure similar to that shown to be safe and effective in adult patients.

4.4.2 Values, preferences and acceptability (Web Annex D)

The assessment of the Guidelines Development Group was that, given the marked benefits relative to harms, the recommendations were not sensitive to preferences. An online survey was distributed between August and September 2021 to global, regional and national networks of paediatricians treating HCV-infected children and adolescents. The survey assessed preferences and acceptability regarding which children to treat and prioritize and which DAA regimens to use. Networks included: PENTA Child Health network and the Federation of International Societies of Paediatric Gastroenterology, Hepatology and Nutrition (FISPGHAN) and its regional counterparts – the Asian Pan-Pacific Society (APPSPGHAN); the Commonwealth Association of Paediatric Gastroenterology and Nutrition (CAPGAN); the European Society (ESPGHAN); the Latin American Society (LASPGHAN); the North America Society (NASPGHAN); and the Pan Arab Society (PASPGHAN). Some 142 health care workers responded, of whom 94 had treated HCV-infected for children or adolescents in the preceding three years. All WHO geographic regions were represented among respondents; the highest proportions of respondents were from the Western Pacific (43%) and the Americas (19%). It was not possible to survey end-users such as parents, care-givers or the children themselves, as there is still very limited routine testing and case-finding of children, and therefore most parents would be unaware their child is infected. Even fewer have experience of their child being treated.

Preferences for treating different age groups: The majority (94%) reported strong support for treating (defined as very likely or likely to treat) adolescents (ages 12–17 years), and 81% expressed support for treating those ages 6–11 years; but slightly less (at 60%) supported treating children ages 3–5 years. The most common reasons cited for not treating younger age groups included: the chance of spontaneous clearance (27%), slower disease progression and asymptomatic disease in early childhood (24%), limited clinical trial data (15%), lack of country drug approvals and registration for DAA regimens in younger age groups (22%) and difficulties with administering medication to young children (12%). The majority of respondents (59%) supported inclusion of treatment recommendations in the guidelines for children 3 years of age and older. A further 15% supported inclusion of treatment recommendations only for older children (≥6 years) and adolescents, and 22% supported treatment for adolescents only.

Preferences for choice of regimen: The most commonly used and preferred DAA regimens for treatment across all age groups among 82 health care workers who reported recent treatment experience were: sofosbuvir/ledipasvir (52% for adolescents and 28% for older children); sofosbuvir/velpatasvir (32% for adolescents and 20% for older children); and glecaprevir/ pibrentasvir (23% for adolescents and 10% for older children). The main reason for their use, given by 95% of respondents, was drug availability, because they were the most commonly available regimens at the respondents' facilities. Other reasons included: good safety data (95%), professional society guidelines recommending their use (88%), suitability of a regimen to treat HCV genotypes prevalent in the country (including pangenotypic) (84%) and high efficacy (72%).

Although there was no commissioned survey of end-users – that is, either parents or HCV infected children/adolescents, previous surveys have indicated that curative, short-course (that is, 8–12 weeks) oral DAA treatment is highly acceptable to adolescents and children, as well as to their parents or caregivers *(96)*, because of the high likelihood of a cure, and minimal adverse events compared with interferon injections. Cure will enable adolescents and children to live free of a socially stigmatizing infection. It is recognized that some younger children may have issues with palatability, especially if the medication is available only in tablet form, as is sofosbuvir/ daclatasvir.

Referenzen aus Leitlinien

67. Indolfi G, Easterbrook P, Dusheiko G, El-Sayed MH, Jonas MM, Thorne C et al. Hepatitis C virus infection in children and adolescents. Lancet Gastroenterol Hepatol. 2019;4:477-87. doi: 10.1016/s2468-1253(19)30046-9

68. Malik F, Bailey H, Chan P, Collins IJ, Mozalevskis A, Thorne C et al. Where are the children innational hepatitis C policies? A global review of national strategic plans and guidelines. JHEP Rep. 2021;3:100227. doi: 10.1016/j.jhepr.2021.100227

69. Schmelzer J, Dugan E, Blach S, Coleman S, Cai Z, DePaola M et al. Global prevalence of hepatitis C virus in children in 2018: a modelling study. Lancet Gastroenterol Hepatol. 2020;5:374-92. doi: 10.1016/s2468-1253(19)30385-1

70. Indolfi G, Hierro L, Dezsofi A, Jahnel J, Debray D, Hadzic N et al. Treatment of Chronic Hepatitis C Virus Infection in Children: A Position Paper by the Hepatology Committee of European Society of Paediatric Gastroenterology, Hepatology and Nutrition. J Pediatr Gastroenterol Nutr. 2018;66:505-15. doi: 10.1097/mpg.0000000000001872

71. Modin L, Arshad A, Wilkes B, Benselin J, Lloyd C, Irving WL et al. Epidemiology and natural history of hepatitis C virus infection among children and young people. J Hepatol. 2019;70:371-8.
72. Serranti D, Dodi I, Nicastro E, Cangelosi AM, Riva S, Ricci S et al. Shortened 8-Week Course of Sofosbuvir/Ledipasvir Therapy in Adolescents With Chronic Hepatitis C Infection. J Pediatr Gastroenterol Nutr. 2019;69:595-8. doi: 10.1097/mpg.0000000000002449
73. Murray KF, Balistreri WF, Bansal S, Whitworth S, Evans HM, Gonzalez-Peralta RP et al. Safety and Efficacy of Ledipasvir-Sofosbuvir With or Without Ribavirin for Chronic Hepatitis C in Children Ages 6-11. Hepatology. 2018;68:2158-66. doi: 10.1002/hep.30123
74. Rosenthal P, Schwarz KB, Gonzalez-Peralta RP, Lin CH, Kelly DA, Nightingale S et al. Sofosbuvir and Ribavirin Therapy for Children Aged 3 to <12 Years With Hepatitis C Virus Genotype 2 or 3 Infection. Hepatology. 2020;71:31-43. doi: 10.1002/hep.30821
75. Mack CL, Gonzalez-Peralta RP, Gupta N, Leung D, Narkewicz MR, Roberts EA et al. NASPGHAN practice guidelines: Diagnosis and management of hepatitis C infection in infants, children, and adolescents. J Pediatr Gastroenterol Nutr. 2012;54:838-55. doi: 10.1097/MPG.0b013e318258328d
76. Druyts E, Thorlund K, Wu P, Kanters S, Yaya S, Cooper CL et al. Efficacy and safety of pegylated interferon alfa-2a or alfa-2b plus ribavirin for the treatment of chronic hepatitis C in children and adolescents: a systematic review and meta-analysis. Clin Infect Dis. 2013;56:961-7. doi: 10.1093/cid/cis1031
77. Wirth S, Pieper-Boustani H, Lang T, Ballauff A, Kullmer U, Gerner P et al. Peginterferon alfa- 2b plus ribavirin treatment in children and adolescents with chronic hepatitis C. Hepatology. 2005;41:1013-8. doi: 10.1002/hep.20661
78. Wirth S, Ribes-Koninckx C, Calzado MA, Bortolotti F, Zancan L, Jara P et al. High sustained virologic response rates in children with chronic hepatitis C receiving peginterferon alfa-2b plus ribavirin. J Hepatol. 2010;52:501-7. doi: 10.1016/j.jhep.2010.01.016
79. Jara P, Hierro L, de la Vega A, Diaz C, Camarena C, Frauca E et al. Efficacy and safety of peginterferon-alpha2b and ribavirin combination therapy in children with chronic hepatitis C infection. Pediatr Infect Dis J. 2008;27:142-8. doi: 10.1097/INF.0b013e318159836c
80. Sokal EM, Bourgois A, Stephenne X, Silveira T, Porta G, Gardovska D et al. Peginterferon alfa- 2a plus ribavirin for chronic hepatitis C virus infection in children and adolescents. J Hepatol. 2010;52:827-31. doi: 10.1016/j.jhep.2010.01.028
81. Tajiri H, Inui A, Kiyohara Y, Suzuki M, Kagimoto S, Etani Y et al. Peginterferon alpha-2b and ribavirin for the treatment of chronic hepatitis C in Japanese pediatric and young adult patients: a survey of the Japan Society of Pediatric Hepatology. Eur J Gastroenterol Hepatol. 2009;21:1256-60. doi: 10.1097/MEG.0b013e32832a4e97
82. Baker RD, Dee D, Baker SS. Response to pegylated interferon alpha-2b and ribavirin in children with chronic hepatitis C. J Clin Gastroenterol. 2007;41:111-4. doi: 10.1097/MCG.0b013e31802dd2f6
83. Indolfi G, Nebbia G, Cananzi M, Maccabruni A, Zaramella M, D'Antiga L et al. Kinetic of Virologic Response to Pegylated Interferon and Ribavirin in Children With Chronic Hepatitis C Predicts the Effect of Treatment. Pediatr Infect Dis J. 2016;35:1300-3. doi: 10.1097/inf.0000000000001325
84. Balistreri WF, Murray KF, Rosenthal P, Bansal S, Lin CH, Kersey K et al. The safety and effectiveness of ledipasvir-sofosbuvir in adolescents 12-17 years old with hepatitis C virus genotype 1 infection. Hepatology. 2017;66:371-8. doi: 10.1002/hep.28995
85. Wirth S, Rosenthal P, Gonzalez-Peralta RP, Jonas MM, Balistreri WF, Lin CH et al. Sofosbuvir and ribavirin in adolescents 12-17 years old with hepatitis C virus genotype 2 or 3 infection. Hepatology. 2017;66:1102-10. doi: 10.1002/hep.29278
86. Garrison KL, Mathias A, Kersey K, Kanwar B, Ni L, Jain A et al. Pharmacokinetics of oncedaily sofosbuvir and ledipasvir/sofosbuvir in CV-infected pediatrics aged 6 to <12 years old. 2016;64:361-601. doi: https://doi.org/10.1002/hep.28798
87. Yakoot M, El-Shabrawi MH, AbdElgawad MM, Mahfouz AA, Helmy S, Abdo AM et al. Dual sofosbuvir/daclatasvir therapy in adolescent patients with chronic hepatitis C infection. J Pediatr Gastroenterol Nutr. 2018;67:86-9. doi: 10.1097/mpg.0000000000001968
88. Abdel Ghaffar TY, El Naghi S, Abdel Gawad M, Helmy S, Abdel Ghaffar A, Yousef M et al. Safety and efficacy of combined sofosbuvir/daclatasvir treatment of children and adolescents with chronic hepatitis C Genotype 4. J Viral Hepat. 2019;26:263-70. doi: 10.1111/jvh.13032
89. Bristol-Myers Squibb. Important information about the discontinuation of Daklinza: Bristol- Myers Squibb; 2020 (https://www.bms.com/assets/bms/brazil/documents/INFORMATIVO%20DAKLINZA%20final.pdf, accessed 20 March 2022).
90. Jonas MM, Squires RH, Rhee SM, Lin CW, Bessho K, Feiterna-Sperling C et al. Pharmacokinetics, safety, and efficacy of glecaprevir/pibrentasvir in adolescents with chronic hepatitis C virus: Part 1 of the DORA Study. Hepatol. 2020;71:456-62. doi: 10.1002/hep.30840
91. Jonas MM, Rhee S, Kelly DA, Del Valle-Segarra A, Feiterna-Sperling C, Gilmour S et al. Pharmacokinetics, Safety, and Efficacy of Glecaprevir/Pibrentasvir in Children With Chronic HCV: Part 2 of the DORA Study. Hepatology. 2021;74:19-27. doi: 10.1002/hep.31841

92. Hirsch C, Badue Pereira MF, Bernardes T, Palandri G, Fink T, Benevides G et al. Direct-acting antivirals for children with chronic hepatitis C: a Brazilian single center experience. ESPID Meeting 2020: European Society for Paediatric Infectious Diseases; 2020.
93. Rodrigue JR, Balistreri W, Haber B, Jonas MM, Mohan P, Molleston JP et al. Impact of hepatitis C virus infection on children and their caregivers: quality of life, cognitive, and emotional outcomes. J Pediatr Gastroenterol Nutr. 2009;48:341-7. doi: 10.1097/MPG.0b013e318185998f
94. Tehranian S, Jafari S, Yousofi J, Kiani M, Seyedin S, Khakshour A et al. Health-related quality of life (HRQOL) in children with chronic liver disease in North East Iran using PedsQL™ 4.0. Electron Physician. 2015;7:1214-9. doi: 10.14661/2015.1214-1219
95. Nydegger A, Srivastava A, Wake M, Smith AL, Hardikar W. Health-related quality of life in children with hepatitis C acquired in the first year of life. J Gastroenterol Hepatol. 2008;23:226-30. doi: 10.1111/j.1440-1746.2007.04859.x
96. Younossi ZM, Stepanova M, Balistreri W, Schwarz K, Murray KF, Rosenthal P et al. Health-related quality of life in adolescent patients with hepatitis C genotype 1 treated with sofosbuvir and ledipasvir. J Pediatr Gastroenterol Nutr. 2018;66:112-6. doi: 10.1097/mpg.0000000000001754
97. Younossi ZM, Stepanova M, Schwarz KB, Wirth S, Rosenthal P, Gonzalez-Peralta R et al. Quality of life in adolescents with hepatitis C treated with sofosbuvir and ribavirin. J Viral Hepat. 2018;25:354-62. doi: 10.1111/jvh.12830
98. U.S. Food and Drug Administration. Chronic hepatitis C virus infection: developing direct-acting antiviral drugs for treatment guidance for industry. Silver Spring (MD): U.S. Food and Drug Administration; 2017 (https://www.fda.gov/media/79486/download, accessed 30 March 2022).
99. Al-Nahari MM, Abbassi MM, Ebeid FS, Hassany M, El-Sayed MH, Farid SF. Pharmacokinetics of daclatasvir in Egyptian adolescents with genotype-4 HCV infection. Antivir Ther. 2020;25:101- 10. doi: 10.3851/imp3357
100. Chan P, Li H, Zhu L, Bifano M, Eley T, Osawa M et al. Population Pharmacokinetic Analysis of Daclatasvir in Subjects with Chronic Hepatitis C Virus Infection. Clin Pharmacokinet. 2017;56:1173-83. doi: 10.1007/s40262-016-0504-2
101. Cressey TR, Abbassi M, Lallemant M, Indolfi G, Al-Nahari M, Farid S et al. Effective and safe daclatasvir drug exposures predicted in children using adult formulations. Pediatr Infect Dis J. 2021;40:1081-6.
102. National Institutes of Health. Safety and efficacy of sofosbuvir + ribavirin in adolescents and children with genotype 2 or 3 chronic HCV infection Washington (DC): National Institutes of Health; 2019 (https://clinicaltrials.gov/ct2/show/NCT02175758, accessed 30 March 2022).
103. Rosenthal P, Schwarz K, Gonzalez-Peralta RP, Lin CH, Kelly D, Nightingale S et al. Sofosbuvir + ribavirin for 12 or 24 weeks is safe and effective in children 3 to <12 years old with genotype 2 or genotype 3 chronic hepatitis C infection [Poster 1844]. Hepatology. 2018;68:184-1353. doi: https://doi.org/10.1002/hep.30257
104. Begley R, Meng A, Massetto B, Shao J, Ling J, Mathias A. Pharmacokinetics of once daily sofosbuvir or ledipasvir/sofosbuvir in HCV-infected pediatrics aged 3 to <6 years old. Hepatology. 2018;68:184-1354. doi: https://aasldpubs.onlinelibrary.wiley.com/doi/full/10.1002/hep.30257
105. Haber B, Alonso E, Pedreira A, Rodriguez-Baez N, Ciocca M, Lacaille F et al. Long-Term Follow-Up of Children Treated With Peginterferon and Ribavirin for Hepatitis C Virus Infection. J Pediatr Gastroenterol Nutr. 2017;64:89-94. doi: 10.1097/mpg.0000000000001239
106. Molleston JP, Mellman W, Narkewicz MR, Balistreri WF, Gonzalez-Peralta RP, Jonas MM et al. Autoantibodies and autoimmune disease during treatment of children with chronic hepatitis C. J Pediatr Gastroenterol Nutr. 2013;56:304-10. doi: 10.1097/MPG.0b013e3182774cae
107. Narkewicz MR, Rosenthal P, Schwarz KB, Drack A, Margolis T, Repka MX. Ophthalmologic complications in children with chronic hepatitis C treated with pegylated interferon. J Pediatr Gastroenterol Nutr. 2010;51:183-6. doi: 10.1097/MPG.0b013e3181b99cf0
108. Zheng Y, Wang Z, Xie Z, Dai R, Zhou Z. Fulminant type 1 diabetes caused by peginterferon -2a therapy in hepatitis C. J Diabetes. 2018;10:419-20. doi: 10.1111/1753-0407.12636
109. Walzer N, Flamm SL. Pegylated IFN- and ribavirin: emerging data in the treatment of special
110. Bortolotti F, Verucchi G, Camma C, Cabibbo G, Zancan L, Indolfi G et al. Long-term course of chronic hepatitis C in children: from viral clearance to end-stage liver disease. Gastroenterol. 2008;134:1900-7. doi: 10.1053/j.gastro.2008.02.082
111. Badizadegan K, Jonas MM, Ott MJ, Nelson SP, Perez-Atayde AR. Histopathology of the liver in children with chronic hepatitis C viral infection. 1998;28:1416-23. doi: https://doi.org/10.1002/hep.510280534
112. European Medicines Agency. Personal communication, EMA/127791/2019. 2019:2. (https://7516e5c8-88e8-4634-85db-70d27ff1f169.filesusr.com/ugd/38bdff_204c9b65a0bc4aca8cc51e29f09628ee.pdf, accessed 30 March 2022).

4 Detaillierte Darstellung der Recherchestrategie

Cochrane Library - Cochrane Database of Systematic Reviews (Issue 07 of 12, July 2025) am 21.07.2025

#	Suchschritt
1	[mh "Hepatitis C"]
2	(Hepatitis NEAR/3 C):ti,ab,kw
3	HCV:ti,ab,kw
4	[mh Hepacivirus]
5	Hepacivirus:ti,ab,kw
6	#1 OR #2 OR #3 OR #4 OR #5
7	#6
8	#7
9	#7 NOT #8

Leitlinien und systematische Reviews in PubMed am 21.07.2025

verwendeter Suchfilter für Leitlinien ohne Änderung:
Konsentierter Standardfilter für Leitlinien (LL), Team Informationsmanagement der Abteilung Fachberatung Medizin, Gemeinsamer Bundesausschuss, letzte Aktualisierung am 21.06.2017.

verwendeter Suchfilter für systematische Reviews ohne Änderung:
Konsentierter Standardfilter für Systematische Reviews (SR), Team Informationsmanagement der Abteilung Fachberatung Medizin, Gemeinsamer Bundesausschuss, letzte Aktualisierung am 15.01.2025.

#	Suchschritt
	Leitlinien
1	"Hepatitis C"[mh]
2	"Hepatitis C"[tiab:~3]
3	HCV[tiab]
4	Hepacivirus[mh]
5	Hepacivirus[tiab]
6	#1 OR #2 OR #3 OR #4 OR #5
7	(#6) AND (Guideline[ptyp] OR Practice Guideline[ptyp] OR guideline*[ti] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp] OR recommendation*[ti])
8	(#7) AND ("2020/07/01"[PDAT] : "3000"[PDAT])
9	(#8) NOT ("retracted publication"[pt] OR "retraction notice"[pt] OR "retraction of publication"[pt] OR "preprint"[pt])
	systematische Reviews

#	Suchschritt
10	(#6) AND ("systematic review"[pt] OR "meta-analysis"[pt] OR "network meta-analysis"[mh] OR "network meta-analysis"[pt] OR (systematic*[tiab] AND (review*[tiab] OR overview*[tiab])) OR metareview*[tiab] OR umbrella review*[tiab] OR "overview of reviews"[tiab] OR meta-analy*[tiab] OR metaanaly*[tiab] OR metanaly*[tiab] OR meta-synthes*[tiab] OR metasynthes*[tiab] OR meta-study[tiab] OR metastudy[tiab] OR integrative review[tiab] OR integrative literature review[tiab] OR evidence review[tiab] OR (("evidence-based medicine"[mh] OR evidence synthes*[tiab]) AND "review"[pt]) OR ((("evidence based"[tiab:~3]) OR evidence base[tiab]) AND (review*[tiab] OR overview*[tiab])) OR (review[ti] AND (comprehensive[ti] OR studies[ti] OR trials[ti])) OR ((critical appraisal*[tiab] OR critically appraise*[tiab] OR study selection[tiab] OR ((predetermined[tiab] OR inclusion[tiab] OR selection[tiab] OR eligibility[tiab]) AND criteri*[tiab]) OR exclusion criteri*[tiab] OR screening criteri*[tiab] OR systematic*[tiab] OR data extraction*[tiab] OR data synthes*[tiab] OR prisma*[tiab] OR moose[tiab] OR entreq[tiab] OR mecir[tiab] OR stard[tiab] OR strobe[tiab] OR "risk of bias"[tiab]) AND (survey*[tiab] OR overview*[tiab] OR review*[tiab] OR search*[tiab] OR analysis[ti] OR apprais*[tiab] OR research*[tiab] OR synthes*[tiab]) AND (literature[tiab] OR articles[tiab] OR publications[tiab] OR bibliographies[tiab] OR published[tiab] OR citations[tiab] OR database*[tiab] OR references[tiab] OR reference-list*[tiab] OR papers[tiab] OR trials[tiab] OR studies[tiab] OR medline[tiab] OR embase[tiab] OR cochrane[tiab] OR pubmed[tiab] OR "web of science" [tiab] OR cinahl[tiab] OR cinhal[tiab] OR scisearch[tiab] OR ovid[tiab] OR ebsco[tiab] OR scopus[tiab] OR epistemonikos[tiab] OR prospero[tiab] OR proquest[tiab] OR lilacs[tiab] OR biosis[tiab])) OR "technical report"[pt] OR HTA[tiab] OR technology assessment*[tiab] OR technology report*[tiab])
11	(#10) AND ("2020/07/01"[PDAT] : "3000"[PDAT])
12	(#11) NOT "The Cochrane database of systematic reviews"[Journal]
13	(#12) NOT ("retracted publication"[pt] OR "retraction notice"[pt] OR "retraction of publication"[pt] OR "preprint"[pt])
	systematische Reviews ohne Leitlinien
14	(#13) NOT (#9)
15	(#14) AND ("2023/07/01"[PDAT] : "3000"[PDAT])
16	#14 NOT #15

Iterative Handsuche nach grauer Literatur, abgeschlossen am 22.07.2025

- Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF)
- National Institute for Health and Care Excellence (NICE)
- Scottish Intercollegiate Guideline Network (SIGN)
- World Health Organization (WHO)
- ECRI Guidelines Trust (ECRI)
- Dynamed / EBSCO
- Guidelines International Network (GIN)
- Trip Medical Database

Referenzen

1. **American Association for the Study of the Liver (AASLD), Infectious Diseases Society of America (IDSA).** HCV guidance: recommendations for testing, managing, and treating hepatitis C [online]. Alexandria (USA): AASLD; 2023. [Zugriff: 22.07.2025]. URL: https://www.hcvguidelines.org/sites/default/files/full-guidance-pdf/AASLD-IDSA_HCVGuidance_December_19_2023.pdf.
2. **Bhattacharya D, Aronsohn A, Price J, Lo Re V.** Hepatitis C guidance 2023 update: AASLD-IDSA recommendations for testing, managing, and treating hepatitis C virus infection. Clin Infect Dis 2023(May):ciad319.
3. **Indolfi G, Easterbrook P, Giometto S, Malik F, Chou R, Lucenteforte E.** Efficacy and safety of DAA in children and adolescents with chronic HCV infection: a systematic review and meta-analysis. Liver Int 2024;44(3):663-681.
4. **World Health Organization (WHO).** Updated recommendations on treatment of adolescents and children with chronic HCV infection, and HCV simplified service delivery and diagnostics [online]. Genf (SUI): WHO; 2022. [Zugriff: 21.07.2025]. URL: https://iris.who.int/bitstream/handle/10665/363590/9789240052734-eng.pdf?sequence=1.

[A] **Rethlefsen ML, Kirtley S, Waffenschmidt S, Ayala AP, Moher D, Page MJ, et al.** PRISMA-S: an extension to the PRISMA Statement for Reporting Literature Searches in Systematic Reviews. Syst Rev 2021;10(1):39. https://doi.org/10.1186/s13643-020-01542-z

[B] **McGowan J, Sampson M, Salzwedel DM, Cogo E, Foerster V, Lefebvre C.** PRESS Peer Review of Electronic Search Strategies: 2015 Guideline Statement. J Clin Epidemiol 2016;75:40-46. https://doi.org/10.1016/j.jclinepi.2016.01.021

Beteiligung von Fachgesellschaften und der AkdÄ zu Fragen der Vergleichstherapie nach §35a Abs. 7 SGB V i.V.m. VerfO 5. Kapitel § 7 Abs. 6

Verfahrens-Nr.: 2025-B-197

Verfasser	
Name der Institution	Arzneimittelkommission der deutschen Ärzteschaft (AkdÄ), Bundesärztekammer, Dezernat 6 – Wissenschaft, Forschung und Ethik, Herbert-Lewin-Platz 1, 10623 Berlin (www.akdae.de)
Datum der Erstellung	20. August 2025

(Bei mehreren beteiligten Fachgesellschaften bitte mit entsprechenden Angaben.)

Indikation
Behandlung der akuten und chronischen Hepatitis-C-Virus (HCV)-Infektion bei Erwachsenen, Jugendlichen und Kindern ab 3 Jahren
Fragen zur Vergleichstherapie
Was ist der Behandlungsstandard in o. g. Indikation unter Berücksichtigung der vorliegenden Evidenz? Wie sieht die Versorgungspraxis in Deutschland aus?

Vorbemerkung:
Die Behandlung der chronischen Hepatitis-C-Virus(HCV)-Infektion hat sich mit der Einführung der direkten antiviralen Wirkstoffe (DAA) gegen Hepatitis C im Jahre 2014 entscheidend geändert. Die EU hat mit Sofosbuvir im Januar 2014 den ersten nukleotidischen Polymerase-Inhibitor (= NS5B-Inhibitor) zugelassen, der eine Heilung der Krankheit ermöglichte. Weitere DAA zur Behandlung der Hepatitis C wurden mit Simeprevir im Mai und mit Daclatasvir im August 2014 zugelassen. Vorher, d. h. bis 2013, bestand die Standardbehandlung aus der kombinierten Gabe eines Peg-alfa-Interferons mit Ribavirin, im Fall von Genotyp 1 ergänzt um ein Medikament aus der Klasse der HCV-Protease-Inhibitoren. Bis dahin war das Therapieziel, die Progression der Krankheit bis hin zur Leberzirrhose und zum Leberversagen zu verhindern. Mit den DAA ist das Ziel der Therapie, die HCV-Infektion zu heilen (Sustained Viral Response, SVR). Entsprechend wurde der Behandlungsstandard mit Kombinationen angepasst und die Leitlinie 2018 aktualisiert (1, 2).

Mit der Zulassung von DAA bei Kindern ab 3 Jahren können seit 2020 auch Kleinkinder erfolgreich mit DAA behandelt werden (3). Somit stehen für alle HCV-Genotypen und praktisch alle Therapiekonstellationen effektive Medikamente und Arzneimittelkombinationen zur Behandlung der chronischen HCV-Infektion zur Verfügung. Es ist erklärtes Ziel, die Hepatitis C bis 2030 zu eliminieren (4). Die Optionen für Kinder ab 3 Jahren und Jugendliche sind durch neue Zulassungen in den entsprechenden Altersklassen belegt (3).

Folgende Substanzklassen zur Behandlung der HCV-Infektion stehen heute zur Verfügung (1, 2):

1. NS3/4A-Protease-Inhibitoren (Substanzname endet auf „previr“), wie Glecaprevir, Grazoprevir, Voxilaprevir

2. NS5A-Inhibitoren (Substanzname endet auf „asvir“), wie Elbasvir, Ledipasvir, Pibrentasvir, Velpatasvir
3. NS5B-Inhibitoren (HCV-RNA-Polymerase-Inhibitoren, Substanzname endet auf „buvir“), wie Sofosbuvir
4. Nukleosidanalogon (RNA-Polymerase-Inhibitor), wie Ribavirin

Behandlung der Hepatitis C (Kinder ab 3 Jahre, Jugendliche und Erwachsene):

Mittel der ersten Wahl sind nach Diagnosestellung bei Patienten ohne dekompensierte Zirrhose und ohne fortgeschrittene Niereninsuffizienz die Kombination von Glecaprevir plus Pibrentasvir oder von Velpatasvir plus Sofosbuvir (2).

Glecaprevir plus Pibrentasvir (Maviret® 50 mg/20 mg überzogenes Granulat im Beutel) ist zugelassen zur Behandlung der chronischen HCV-Infektion der Genotypen 1 bis 6 bei Kindern ab einem Alter von 3 Jahren (5). Für Erwachsenen sind Filmtabletten (Maviret® 100 mg/40 mg Filmtabletten) erhältlich.

Velpatasvir plus Sofosbuvir (Epclusa® befilmtes Granulat im Beutel) ist zugelassen zur Behandlung der chronischen HCV-Infektion bei Patienten ab einem Alter von 3 Jahren (6). Für Erwachsene und Jugendliche stehen Epclusa® Filmtabletten (400 mg/100 mg und 200 mg und 50 mg) zur Verfügung.

Alternativ erhalten Patienten mit einer HCV-Genotyp-1- oder -4-Infektion ohne dekompensierte Zirrhose und ohne fortgeschrittene Niereninsuffizienz auch eine Kombination von Grazoprevir plus Elbasvir oder eine Kombination von Ledipasvir plus Sofosbuvir.

Grazoprevir plus Elbasvir (Zepatier® 50 mg/100 mg Filmtabletten) ist zugelassen zur Behandlung der chronischen HCV-Infektion bei Erwachsenen, Jugendlichen und Kindern ab einem Alter von 12 Jahren und einem Körpergewicht von mindestens 30 kg (7).

Ledipasvir plus Sofosbuvir (Harvoni® befilmtes Granulat im Beutel) ist zugelassen zur Behandlung der chronischen HCV-Infektion bei Erwachsenen, Kindern und Jugendlichen ab einem Alter von 3 Jahren (8). Für Jugendliche und Erwachsene stehen Filmtabletten (90 mg/400 mg und 45 mg/200 mg) zur Verfügung.

Patienten mit Versagen auf eine vorherige DAA-Therapie sollen unter Berücksichtigung des Vortherapiestatus, der Komedikation und gegebenenfalls von Komorbiditäten mit folgender Therapie behandelt werden: Voxilaprevir, Velpatasvir und Sofosbuvir.

Voxilaprevir, Velpatasvir und Sofosbuvir (Vosevi® Filmtabletten) sind zugelassen zur Behandlung der chronischen HCV-Infektion bei Patienten ab einem Alter von 12 Jahren und mit einem Körpergewicht von mindestens 30 kg (9). Die Dreifachkombination ist in zwei Dosisstärken erhältlich (400 mg Sofosbuvir, 100 mg Velpatasvir und 100 mg Voxilaprevir bzw. 200 mg Sofosbuvir, 50 mg Velpatasvir und 50 mg Voxilaprevir).

Für Patienten mit einem Therapieversagen auf die Gabe der Dreifachkombination von Voxilaprevir plus Velpatasvir und Sofosbuvir wird eine erneute Therapie auf der Grundlage einer Resistenzanalyse empfohlen (2). Unter Umständen kommt auch dann Ribavirin zur Anwendung.
Ribavirin (Ribavirin-ratiopharm® 200 mg/400 mg Filmtabletten) ist zugelassen in Kombination mit anderen Arzneimitteln zur Behandlung der chronischen HCV-Infektion bei vorbehandelten Erwachsenen (10). Für die für Kinder zugelassenen Darreichungsformen von Ribavirin (Rebetol® 40 mg/ml Lösung, Rebetol 200 mg Hartkapseln) wurde auf Antrag des Zulassungsinhabers Merck Sharp &

Dohme B.V. von der Europäischen Kommission die Marktzulassung am 18.10.2023 widerrufen (11). Grund der Rücknahme waren wirtschaftliche Gründe.

Auch internationale Leitlinien decken sich mit den Empfehlungen in deutschen Leitlinien (12, 13). Der Berufsverband Niedergelassener Gastroenterologen Deutschlands e.V. hat die Therapie der HCV-Infektion gut zusammengefasst (14).

Studien mit direkten antiviralen Wirkstoffen für Kleinkinder
In einer prospektiven Studie erhielten 34 drei bis unter sechs Jahre alte Kinder mit chronischer Hepatitis C mit Genotyp 1 (n = 33) oder Genotyp 4 (n = 1) Ledipasvir-Sofosbuvir-Granulat (33,75 mg/150 mg bei einem Körpergewicht von < 17 kg (zehn Patienten, 29 %) oder 45 mg/200 mg bei einem Körpergewicht von ≥ 17 kg) für zwölf Wochen (15). Zwölf Wochen nach Therapieende (SVR12) wurde eine vollständige Remission bei 33 von 34 (97 %) Kindern erreicht. Ein Patient beendete nach fünf Tagen die Behandlung wegen schlechtem Geschmack. Über alle Altersgruppen wurden 222 von 226 Patienten (98 %) erfolgreich behandelt. Diese Daten zeigen im Vergleich zu der früher üblichen Kombination Ribavirin plus Peginterferon alfa-2a eine deutlich bessere Ansprechrate.

Kombination Glecaprevir/Pibrentasvir wurde bei Kindern im Alter ab 3 Jahren und älter zur Behandlung der chronischen HCV-Infektion untersucht und zugelassen (5, 16). Bei der Kohorte der Kleinkinder (3 bis < 6 Jahre alt) waren 23/24 (96 %) nach einer achtwöchigen Therapie geheilt (16).

Gibt es Kriterien für unterschiedliche Behandlungsentscheidungen in der o. g. Indikation, die regelhaft berücksichtigt werden? Wenn ja, welche sind dies und was sind in dem Fall die Therapieoptionen?

Für Patienten mit fortgeschrittener Leberzirrhose kommen unter Berücksichtigung der bisherigen Therapie, der Komedikation und gegebenenfalls von Komorbiditäten folgende Therapieoptionen infrage: Velpatasvir plus Sofosbuvir ± Ribavirin oder Ledipasvir plus Sofosbuvir ± Ribavirin beim HCV-Genotyp 1 oder 4. Regime mit Protease-Inhibitoren (NS3/4A-Protease-Inhibitoren wie Glecaprevir, Grazoprevir oder Voxilaprevir) werden bei dekompensierter Zirrhose nicht empfohlen (1, 2).

Für Patienten mit fortgeschrittener Niereninsuffizienz (GFR < 30 ml/min bzw. Dialyse) gibt es unter Berücksichtigung der bisherigen Therapie und der Komedikation und gegebenenfalls von Komorbiditäten folgende Therapiemöglichkeiten: Glecaprevir plus Pibrentasvir oder Grazoprevir plus Elbasvir beim HCV-Genotyp 1 oder 4. Bei der zusätzlichen Gabe von Ribavirin ist eine Dosis-anpassung entsprechend der GFR notwendig. Regime mit nukleotidischen Polymerase-Inhibitoren (Sofosbuvir) sollten bei schwerer Niereninsuffizienz vermieden werden (1, 2).

Referenzliste:

1. Zimmermann T, Jansen PL, Sarrazin C, Vollmar J, Zeuzem S. S3-Leitlinie „Prophylaxe, Diagnostik und Therapie der Hepatitis-C-Virus (HCV) -Infektion“. Z Gastroenterol 2018; 56(7):e53-e115. doi: 10.1055/a-0598-5242.
2. Sarrazin C, Zimmermann T, Berg T, Hinrichsen H, Mauss S, Wedemeyer H et al. Prophylaxe, Diagnostik und Therapie der Hepatitis-C-Virus(HCV)-Infektion. Z Gastroenterol 2020; 58(11):1110–31. doi: 10.1055/a-1226-0241.
3. Wirth S, Schreiber-Dietrich D, Dietrich CF. Aktuelle Therapie der chronischen Hepatitis C bei Kindern und Jugendlichen. Monatsschr Kinderheilkd 2021; 169(6):534–41. doi: 10.1007/s00112-021-01122-y.
4. Kim NG, Kullar R, Khalil H, Saab S. Meeting the WHO hepatitis C virus elimination goal: Review of treatment in paediatrics. J Viral Hepat 2020; 27(8):762–9. doi: 10.1111/jvh.13317.

5. AbbVie Deutschland GmbH & Co. KG. Fachinformation „Maviret® 50 mg/20 mg überzogenes Granulat im Beutel“; März 2023.
6. Gilead Sciences Ireland UC. Fachinformation „Epclusa® befilmtes Granulat im Beutel“; August 2023.
7. Merck Sharp & Dohme B.V. Fachinformation „Zepatier® 50 mg/100 mg Filmtabletten“; Juni 2022.
8. Gilead Sciences GmbH. Fachinformation „Harvoni® befilmtes Granulat im Beutel”. Stand November 2022.
9. Gilead Sciences Ireland UC. Fachinformation „Vosevi® Filmtabletten”. Stand August 2023.
10. Ratiopharm GmbH: Fachinformation „Ribavirin-ratiopharm® 200 mg/400 mg Filmtabletten“. Stand Januar 2025.
11. European Medicines Agency: European Public Assessment Report (EPAR): Rebetol (Ribavirin); withdrawn. Verfügbar unter: https://www.ema.europa.eu/en/medicines/human/EPAR/rebetol.
12. EASL recommendations on treatment of hepatitis C: Final update of the series☆. J Hepatol 2020; 73(5):1170–218. doi: 10.1016/j.jhep.2020.08.018.
13. Lagging M, Wejstål R, Duberg A-S, Aleman S, Weiland O, Westin J. Treatment of hepatitis C virus infection for adults and children: updated Swedish consensus guidelines 2017. Infect Dis (Lond) 2018; 50(8):569–83. doi: 10.1080/23744235.2018.1445281.
14. Berufsverband Niedergelassener Gastroenterologen Deutschlands e.V. Empfehlungen des bng zur Therapie der chronischen Hepatitis C. Empfehlung zur Therapie der chronischen Hepatitis C. Update 2024; Stand: Februar 2024. Verfügbar unter: https://bng-gastro.de/wp-admin/admin-ajax.php?juwpfisadmin=false&action=wpfd&task=file.download&wpfd_category_id=111&wpfd_file_id=987498530&token=&preview=1.
15. Schwarz KB, Rosenthal P, Murray KF, Honegger JR, Hardikar W, Hague R et al. Ledipasvir-Sofosbuvir for 12 Weeks in Children 3 to <6 Years Old With Chronic Hepatitis C. Hepatology 2020; 71(2):422–30. doi: 10.1002/hep.30830.
16. Jonas MM, Rhee S, Kelly DA, Del Valle-Segarra A, Feiterna-Sperling C, Gilmour S et al. Pharmacokinetics, Safety, and Efficacy of Glecaprevir/Pibrentasvir in Children With Chronic HCV: Part 2 of the DORA Study. Hepatology 2021; 74(1):19–27. doi: 10.1002/hep.31841.

Ergänzende Stellungnahme vom 01.09.2025 zur Rückfrage des G-BA zur ZVT-Beratung 2025-B-197

Rückfrage des G-BA vom 27.09.2025
„Die Antwort bezieht sich vornehmlich auf die Behandlung der chronischen Hepatitis-C-Infektion. Das fragliche Arzneimittel soll auch für die akute Infektion zugelassen werden. Gibt es Behandlungsstandards, die bei akuter Infektion besonders zu nennen sind? Wie sieht die Versorgungspraxis bei akuter Infektion aus?“

Die Anfangsphase der HCV-Infektion wird **akute Hepatitis C** genannt und ist bzw. war definiert als die ersten sechs Monate nach der ersten Virusexposition. Diese Phase wurde aufgrund der hohen Wahrscheinlichkeit einer spontanen Viruselimination gewählt. Bis jetzt fehlt eine klare, allgemein anerkannte klinische Falldefinition einer akuten Hepatitis C (1-3). Die Unterscheidung einer akuten von einer chronischen Hepatitis C mit einer alleinigen Definition des Nachweises der HCV-Antikörper bzw. der HCV-RNA über mindestens sechs Monate ist klinisch nicht unproblematisch und kann zu einer unnötigen Wartezeit bis zum Beginn einer antiviralen Therapie führen (4).

Meistens verläuft eine HCV-Infektion klinisch stumm und der Beginn ist oft nicht genau bekannt. Nur etwa 20 % der Patienten zeigen Symptome wie Müdigkeit, Appetitlosigkeit, Übelkeit, Erbrechen, Bauchschmerzen und das charakteristische Symptom eines Ikterus (Gelbsucht). Der klinische Verlauf ist zunächst gutartig, und nur wenige Patienten werden stationär behandelt. Ein akutes Leberversagen ist eine seltene Komplikation einer akuten HCV-Infektion (< 1 %) (5). Trotz des primär günstigen Verlaufs entwickeln etwa 50–70 % der Personen mit einer akuten HCV-Infektion eine chronische Infektion, die als anhaltende Virämie über einen Zeitraum von mehr als sechs Monaten definiert ist (1-3).

Kommt es bei einer kürzlich erworbenen HCV-Infektion nach vier Wochen nicht zu einem deutlichen Abfall der HCV-RNA-Konzentration oder ist nach zwölf Wochen noch HCV-RNA nachweisbar, kann von einem Übergang in eine chronische HCV-Erkrankung ausgegangen werden (6, 7). Damit wird heute eine Indikation zur antiviralen Therapie gestellt (1-3).

Die Therapie der sogenannten akuten HCV-Infektion erfolgt grundsätzlich in Analogie zu den Empfehlungen bei einer chronischen HCV-Infektion (1-3). Also sind die Therapieschemata zur Behandlung einer akuten HCV-Infektion mit denen der chronischen HCV-Infektion vergleichbar, aber die Therapiedauer ist kürzer. Schon bei den heute nicht mehr eingesetzten Interferon-basierten Therapien waren die Heilungsraten bei frühen Therapiebeginn besser und die Therapiedauer war kürzer.

In einer deutschen multizentrischen Phase-IV-Therapiestudie zur akuten HCV-Infektion wurde mit einer sechswöchigen Therapie mit Sofosbuvir/Ledipasvir bei HCV-Genotyp-1-infizierten Patienten eine dauerhafte Viruselimination von 100 % erzielt (8).

Somit sind alle Therapieoptionen mit direkten antiviralen Arzneimitteln, die für die chronische Therapie eingesetzt werden, auch für die akute HVC-Infektion geeignet. Das Ziel der Therapie der akuten HCV-Infektion ist identisch mit dem Therapieziel der der chronischen HCV-Infektion, nämlich die dauerhafte Elimination des HCV-Virus.

Folgende Wirkstoffkombinationen werden für die B**ehandlung der akuten Hepatitis C (Kinder ab drei Jahren, Jugendliche und Erwachsene)** eingesetzt:

Mittel der ersten Wahl sind nach Diagnosestellung bei Patienten die Kombination von **Glecaprevir plus Pibrentasvir** oder von **Velpatasvir plus Sofosbuvir**, Alternativ erhalten Patienten mit einer HCV-Genotyp-1- oder -4-Infektion auch eine Kombination von **Grazoprevir plus Elbasvir** oder eine Kombination von **Ledipasvir plus Sofosbuvir** (2).

Da die akute HCV-Infektion nicht gut definiert ist und in eine chronische Phase übergehen kann, wird ein fehlender Abfall der HCV-RNA-Konzentration im Blut nach vier Wochen und die Persistenz der HCV-RNA nach zwölf Wochen heute als Übergang in eine chronische HCV-Erkrankung angesehen. Die Definition akute HCV-Infektion in den ersten sechs Monaten ist somit zu hinterfragen.

Eine spontane Elimination des HCV-Virus sollte vor einem Therapiebeginn abgewartet werden, heute beginnt die Behandlung bei Persistenz des HCV-RNA in der Regel schon nach zwölf Wochen. Ob man den Zeitpunkt des Beginns der antiviralen Therapie dann noch akute oder schon chronische HCV-Infektion nennt, ist von untergeordneter Bedeutung.

Bei Erstdiagnose einer HCV-Infektion mit einer typischen Konstellation für eine chronische Infektion ist ein formales Abwarten einer positiven HCV-RNA über sechs Monate medizinisch nicht erforderlich (3). Eine chronische HCV-Infektion ist bei nachweisbaren HCV-RNA und positiven HCV-Antikörpern klinisch und laborchemisch keine akute (ikterische) Hepatitis und eine Indikation zur antiviralen Therapie (3).

Patienten mit schwerem ikterischem Verlauf und Zeichen eines möglichen Leberversagens werden stationär akut mit den direkten antiviralen Medikamenten behandelt. Dies kommt aber sehr selten vor.

Referenzen:

1. Fasano M, Ieva F, Ciarallo M, Caccianotti B, Santantonio TA. Acute Hepatitis C: Current Status and Future Perspectives. Viruses 2024; 16(11). doi: 10.3390/v16111739.
2. Zeuzem S. Treatment Options in Hepatitis C. Dtsch Arztebl Int 2017; 114(1-02):11–21. doi: 10.3238/arztebl.2017.0011.
3. Sarrazin C, Zimmermann T, Berg T, Hinrichsen H, Mauss S, Wedemeyer H et al. Prophylaxe, Diagnostik und Therapie der Hepatitis-C-Virus(HCV)-Infektion. Z Gastroenterol 2020; 58(11):1110–31. doi: 10.1055/a-1226-0241.
4. Dakic Z, Duric P, Fabri M, O'May F. Validity of hepatitis B and hepatitis C case definitions. J Infect Public Health 2019; 12(4):516–21. doi: 10.1016/j.jiph.2019.01.061.
5. Liu C-H, Kao J-H. Acute hepatitis C virus infection: clinical update and remaining challenges. Clin Mol Hepatol 2023; 29(3):623–42. doi: 10.3350/cmh.2022.0349.
6. Hajarizadeh B, Grebely J, Applegate T, Matthews GV, Amin J, Petoumenos K et al. Dynamics of HCV RNA levels during acute hepatitis C virus infection. J Med Virol 2014; 86(10):1722–9. doi: 10.1002/jmv.24010.
7. Thomson EC, Fleming VM, Main J, Klenerman P, Weber J, Eliahoo J et al. Predicting spontaneous clearance of acute hepatitis C virus in a large cohort of HIV-1-infected men. Gut 2011; 60(6):837–45. doi: 10.1136/gut.2010.217166.

8. Deterding K, Spinner CD, Schott E, Welzel TM, Gerken G, Klinker H et al. Ledipasvir plus sofosbuvir fixed-dose combination for 6 weeks in patients with acute hepatitis C virus genotype 1 monoinfection (HepNet Acute HCV IV): an open-label, single-arm, phase 2 study. Lancet Infect Dis 2017; 17(2):215–22. doi: 10.1016/S1473-3099(16)30408-X.on (HepNet Acute HCV IV): an open-label, single-arm, phase 2 study. Lancet Infect Dis. 2017; 17:215-222. doi: 10.1016/S1473-3099(16)30408-X.