Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

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

Vorgang: 2019-B-123 Ledipasvir/Sofosbuvir (neues Anwendungsgebiet)

Stand: Juni 2019

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

Ledipasvir/Sofosbuvir
[Chronische Hepatitis C bei Kindern]

Kriterien gemäß 5. Kapitel § 6 VerfO	
Sofern als Vergleichstherapie eine Arzneimittelanwendung in Betracht kommt, muss das Arzneimittel grundsätzlich eine Zulassung für das Anwendungsgebiet haben.	*Siehe 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 von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V: • Es liegen keine Beschlüsse im Anwendungsgebiet chronische Hepatitis C bei Patienten im Alter von 3 bis ≤ 11 Jahren vor.
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:	
Ledipasvir/ Sofosbuvir J05AX65 Harvoni®	Geplantes Anwendungsgebiet laut Beratungsanforderung: Behandlung der chronischen Hepatitis C (CHC) bei Kindern zwischen 3 und ≤ 11 Jahren.
Ribavirin J05AB04 Rebetol® Lösung	Rebetol ist in Kombination mit anderen Arzneimitteln bestimmt zur Behandlung der chronischen Hepatitis C (CHC) bei Kindern und Jugendlichen (Kinder ab dem Alter von 3 Jahren und Jugendliche), die nicht vorbehandelt sind und keine Leberdekompensation zeigen (siehe Abschnitte 4.2, 4.4 und 5.1). (Fachinformation Rebetol® Losung zum Einnehmen Stand 02/2019)
Interferon alfa-2b L03AB05 IntronA®	Chronische Hepatitis C: Vor Behandlungsbeginn mit IntronA sollten die Ergebnisse von klinischen Studien zum Vergleich von IntronA mit pegyliertem Interferon berücksichtigt werden (siehe Abschnitt 5.1). *Kinder im Alter ab 3 Jahren und Jugendliche:* IntronA ist, in Kombination mit Ribavirin, bestimmt zur Behandlung von Kindern im Alter von 3 Jahren und älter und Jugendlichen mit chronischer Hepatitis-C-Infektion, die nicht vorbehandelt sind, keine Leberdekompensation zeigen und die HCV-RNA-positiv sind. Bei der Entscheidung, eine Therapie nicht bis zum Erwachsenenalter zu verschieben, ist unbedingt zu berücksichtigen, dass die Kombinationstherapie eine Hemmung des Wachstums induziert, die bei einigen Patienten zu einer reduzierten endgültigen Körpergröße im Erwachsenenalter führte. Die Entscheidung über eine Behandlung sollte von Fall zu Fall abgewogen werden (siehe Abschnitt 4.4). (Fachinformation IntronA® Stand 09/2018)
Peginterferon alfa-2b L03AB10 PegIntron®	*Kinder und Jugendliche (Duale Therapie)* PegIntron ist in Kombination mit Ribavirin bestimmt zur Behandlung von Kindern ab dem Alter von 3 Jahren und Jugendlichen mit chronischer Hepatitis C-Infektion, die nicht vorbehandelt sind, keine Leberdekompensation zeigen und die HCV-RNA-positiv sind. Bei der Entscheidung, eine Therapie nicht bis zum Erwachsenenalter zu verschieben, ist unbedingt zu berücksichtigen, dass die Kombinationstherapie eine Hemmung des Wachstums induzierte, die bei einigen Patienten irreversibel sein kann. Die Entscheidung über eine Behandlung sollte von Fall zu Fall abgewogen werden (siehe Abschnitt 4.4).

II. Zugelassene Arzneimittel im Anwendungsgebiet	
(*nicht in Deutschland im Vertrieb*)	Die Fachinformation zu Ribavirin (Hartkapseln oder Lösung zum Einnehmen) ist zu beachten, wenn PegIntron in Kombination mit Ribavirin angewendet werden soll. *Kinder und Jugendliche (nur duale Therapie) – Dauer der Behandlung:* • *Genotyp 1:* Die empfohlene Behandlungsdauer im Rahmen einer dualen Therapie beträgt 1 Jahr. Eine Extrapolation aus den klinischen Daten zur Kombinationstherapie mit Standard-Interferon bei pädiatrischen Patienten (negativer prädiktiver Wert: 96 % für Interferon alfa-2b/Ribavirin) zeigt, dass es sehr unwahrscheinlich ist, dass Patienten mit nach 12-wöchiger Therapie ausbleibendem virologischen Ansprechen ein virologisches Langzeitansprechen Langzeitansprechen erzielen. Aus diesem Grund wird empfohlen, die Kombinationstherapie mit Peginterferon alfa-2b und Ribavirin bei Kindern und Jugendlichen abzusetzen, wenn die HCV-RNA in Woche 12 um < 2 log10 gegenüber dem Ausgangswert zurückgegangen ist oder wenn in Behandlungswoche 24 HCV-RNA nachweisbar ist. • *Genotyp 2 oder 3:* Die empfohlene Behandlungsdauer im Rahmen einer dualen Therapie beträgt 24 Wochen. • *Genotyp 4:* In der klinischen Studie mit PegIntron/Ribavirin wurden nur 5 Kinder bzw. Jugendliche mit HCV-Genotyp 4 behandelt. Die empfohlene Behandlungsdauer im Rahmen einer dualen Therapie beträgt 1 Jahr. Es wird empfohlen, die Behandlung bei pädiatrischen und jugendlichen Patienten, die PegIntron/Ribavirin erhalten, abzusetzen, wenn die HCV-RNA in Woche 12 um < 2 log10 gegenüber dem Ausgangswert zurückgegangen ist oder wenn in Behandlungswoche 24 HCVRNA nachweisbar ist. (SmPC PegIntron® abgerufen 06/2019)
Peginterferon alfa-2a L03AB11 Pegasys®	<u>Chronische Hepatitis C:</u> *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 fuhren 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). (Fachinformation Pegasys® Stand 03/2018)

Quellen: Fachinformationen

Gemeinsamer Bundesausschuss

Abteilung Fachberatung Medizin

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

Vorgang: 2019-B-123 (Ledipasvir/Sofosbuvir)

Auftrag von:	Abt. AM
Bearbeitet von:	Abt. FB Med
Datum:	26. Juni 2019

Inhaltsverzeichnis

Abkürzungsverzeichnis 3
1 Indikation 4
2 Systematische Recherche....4
3 Ergebnisse....5
3.1 G-BA Beschlüsse/IQWiG Berichte 5
3.2 Cochrane Reviews 7
3.3 Systematische Reviews....7
3.4 Leitlinien....9
4 Detaillierte Darstellung der Recherchestrategie 23
Referenzen 25

Abkürzungsverzeichnis

AASLD	American Association for the Study of Liver Diseases
AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
BSC	Best Supportive Care
CHC	Chronische Hepatitis
CRD	Centre for Reviews and Dissemination
DAA	Directly Acting Antiviral Agents
DGVS	Deutsche Gesellschaft für Gastroenterologie, Verdauungs- und Stoffwechselkrankheiten
EK	Expertenkonsens
G-BA	Gemeinsamer Bundesausschuss
GIN	Guidelines International Network
GoR	Grade of Recommendations
GT	Genotyp
HCV	Hepatitis-C-Virus
HR	Hazard Ratio
HRQoL	Gesundheitsbezogene Lebensqualität
IDSA	Infectious Diseases Society of America
IFN	Interferon
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
LoE	Level of Evidence
NICE	National Institute for Health and Care Excellence
RBV	Ribavirin
RR	Relatives Risiko
SIGN	Scottish Intercollegiate Guidelines Network
SVR	Sustained Virological Response
TRIP	Turn Research into Practice Database
WHO	World Health Organization

1 Indikation

Chronische Hepatitis C bei Kindern und Jugendlichen (0 bis 18 Jahre).

Soweit dies möglich ist, werden 2 Gruppen dargestellt:

- *Kinder zwischen 3 und ≤11 Jahren*
- *Jugendliche zwischen 12 und ≤17 Jahren*

2 Systematische Recherche

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen und evidenzbasierten systematischen Leitlinien zur Indikation *chronische Hepatitis C* durchgeführt. Der Suchzeitraum wurde auf die letzten 5 Jahre eingeschränkt und die Recherche am 06.06.2019 abgeschlossen. Die Suche erfolgte in den aufgeführten Datenbanken bzw. Internetseiten folgender Organisationen: The Cochrane Library (Cochrane Database of Systematic Reviews), MEDLINE (PubMed), AWMF, G-BA, GIN, NICE, TRIP, SIGN, WHO. Ergänzend erfolgte eine freie Internetsuche nach aktuellen deutschen und europäischen Leitlinien. Die detaillierte Darstellung der Suchstrategie ist am Ende der Synopse aufgeführt.

Die Recherche ergab 842 Quellen, die anschließend in einem zweistufigen Screening-Verfahren nach Themenrelevanz und methodischer Qualität gesichtet wurden. Zudem wurde eine Sprachrestriktion auf deutsche und englische Quellen vorgenommen. Insgesamt ergab dies 9 Quellen, die in die synoptische Evidenz-Übersicht aufgenommen wurden.

3 Ergebnisse

3.1 G-BA Beschlüsse/IQWiG Berichte

G-BA, 2018 [3].

Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII - Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V – Ledipasvir/Sofosbuvir (neues Anwendungsgebiet: Chronische Hepatitis C bei Jugendlichen) vom 15. Februar 2018

Neues Anwendungsgebiet (laut Zulassung vom 19. Juli 2017):

Harvoni wird bei Erwachsenen und Jugendlichen im Alter von 12 bis < 18 Jahren zur Behandlung der chronischen Hepatitis C (CHC) angewendet (siehe Abschnitte 4.2, 4.4 und 5.1 der Fachinformation).1

Zur spezifischen Aktivität gegen die verschiedenen Genotypen des Hepatitis-C-Virus (HCV) siehe Abschnitte 4.4 und 5.1 der Fachinformation.

Zweckmäßige Vergleichstherapie

a) Therapienaive Patienten mit chronischer Hepatitis C im Alter von 12 bis < 18 Jahren, Genotypen 1, 4, 5 oder 6

Ribavirin plus Peginterferon alfa

b) Therapienaive Patienten mit chronischer Hepatitis C und kompensierter Zirrhose im Alter von 12 bis < 18 Jahren, Genotyp 3

Ribavirin plus Peginterferon alfa

c) Vorbehandelte Patienten mit chronischer Hepatitis C im Alter von 12 bis < 18 Jahren, Genotypen 1, 4, 5 oder 6

Best-Supportive-Care.

Als „Best-Supportive-Care“ (BSC) wird diejenige Therapie verstanden, die eine bestmögliche, patientenindividuell optimierte, unterstützende Behandlung zur Linderung von Symptomen und Verbesserung der Lebensqualität gewährleistet.

d) Vorbehandelte Patienten mit chronischer Hepatitis C im Alter von 12 bis < 18 Jahren, Genotyp 3

Best-Supportive-Care.

Als „Best-Supportive-Care“ (BSC) wird diejenige Therapie verstanden, die eine bestmögliche, patientenindividuell optimierte, unterstützende Behandlung zur Linderung von Symptomen und Verbesserung der Lebensqualität gewährleistet.

Fazit / Ausmaß des Zusatznutzens / Ergebnis

a) Therapienaive Patienten mit chronischer Hepatitis C im Alter von 12 bis < 18 Jahren, Genotypen 1, 4, 5 oder 6

Anhaltspunkt für einen nicht quantifizierbaren Zusatznutzen.

b) Therapienaive Patienten mit chronischer Hepatitis C und kompensierter Zirrhose im Alter von 12 bis < 18 Jahren, Genotyp 3

Ein Zusatznutzen ist nicht belegt.

c) Vorbehandelte Patienten mit chronischer Hepatitis C im Alter von 12 bis < 18 Jahren, Genotypen 1, 4, 5 oder 6

Anhaltspunkt für einen nicht quantifizierbaren Zusatznutzen.

d) Vorbehandelte Patienten mit chronischer Hepatitis C im Alter von 12 bis < 18 Jahren, Genotyp 3

Ein Zusatznutzen ist nicht belegt.

G-BA, 2018 [2].

Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII - Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V – Sofosbuvir (neues Anwendungsgebiet: Chronische Hepatitis C bei Jugendlichen) vom 5. April 2018

Neues Anwendungsgebiet (laut Zulassung vom 14. September 2017):

Sovaldi wird in Kombination mit anderen Arzneimitteln zur Behandlung der chronischen Hepatitis C (CHC) bei Erwachsenen und bei Jugendlichen im Alter von 12 bis < 18 Jahren angewendet (siehe Abschnitte 4.2, 4.4 und 5.1 der Fachinformation).[1]

Zur spezifischen Aktivität gegen die verschiedenen Genotypen des Hepatitis-C-Virus (HCV) siehe Abschnitte 4.4 und 5.1 der Fachinformation.

[1] Dieser Beschluss bezieht sich ausschließlich auf die am 14. September 2017 zugelassene Patientengruppe der jugendlichen Patienten im Alter von 12 bis <18 Jahren.

Vergleichstherapie

a) Therapienaive Patienten mit chronischer Hepatitis C im Alter von 12 bis < 18 Jahren, Genotypen 2 oder 3

Ribavirin plus Peginterferon alfa

b) Therapieerfahrene Patienten mit chronischer Hepatitis C im Alter von 12 bis < 18 Jahren, Genotypen 2 oder 3

Best-Supportive-Care.

Als „Best-Supportive-Care“ (BSC) wird diejenige Therapie verstanden, die eine bestmögliche, patientenindividuell optimierte, unterstützende Behandlung zur Linderung von Symptomen und Verbesserung der Lebensqualität gewährleistet.

Fazit / Ausmaß des Zusatznutzens / Ergebnis

a) Therapienaive Patienten mit chronischer Hepatitis C im Alter von 12 bis < 18 Jahren, Genotypen 2 oder 3

Anhaltspunkt für einen nicht quantifizierbaren Zusatznutzen.

b) Therapieerfahrene Patienten mit chronischer Hepatitis C im Alter von 12 bis < 18 Jahren, Genotypen 2 oder 3

Anhaltspunkt für einen nicht quantifizierbaren Zusatznutzen.

3.2 Cochrane Reviews

Es wurden keine Cochrane Reviews identifiziert.

3.3 Systematische Reviews

Hartwell D et al., 2014 [4].

The clinical effectiveness and cost-effectiveness of peginterferon alfa and ribavirin for the treatment of chronic hepatitis C in children and young people: a systematic review and economic evaluation

Fragestellung

To assess the clinical effectiveness and cost-effectiveness of peginterferon alfa-2a and peginterferon alfa-2b in combination with RBV, within the licensed indications, for the treatment of chronic HCV in children and young people aged 3–17 years.

Methodik

Population:

- Children and young people aged 3–17 years with compensated chronic HCV of any severity, including those with HIV co-infection and those who were treatment naive or had been previously treated

Intervention:

- peginterferon alfa-2a and peginterferon alfa-2b in combination with RBV

Komparator:

- Best supportive care (e.g. symptomatic treatment, monitoring, treatment without any form of interferon therapy).
- The interventions compared with each other within their licensed indications, i.e. peginterferon alfa-2a and RBV versus peginterferon alfa-2b and RBV.

Endpunkt:

- Studies had to report SVR (defined as undetectable HCV RNA at least 6 months after treatment cessation).
- Studies could also include one or more of the following:
  - virological response to treatment (e.g. during treatment, end of treatment)
  - biochemical response (e.g. ALT)
  - liver inflammation and fibrosis
  - mortality

- adverse effects of treatment, including effects on growth
- HRQoL.

Recherche/Suchzeitraum:

- from database inception to November 2012

Qualitätsbewertung der Studien:

- according to criteria based on those used by the CRD (Centre for Reviews and Dissemination - University of York)

Ergebnisse

Anzahl eingeschlossener Studien: 7 studies reported in 15 publications

[1] Schwarz et al., 2011 Peginterferon alfa-2a
[2] Sokal et al., 2010 Peginterferon alfa-2a, treatment-naive children and adolescents
[3] Al Ali et al., 2010 Peginterferon alfa-2b, treatment-naive patients
[4] Pawlowska et al., 2010 Peginterferon alfa-2b
[5] Wirth et al., 2010 Peginterferon alfa-2b, previously untreated chronic HCV
[6] Ghaffar et al., 2009 Peginterferon alfa-2b
[7] Jara et al., 2008 Peginterferon alfa-2b

Charakteristika der Population:

- In three studies, children who were treatment naïve (see above).

Qualität der Studien:

- Six of the included studies were single-arm, uncontrolled cohort studies and one was a RCT for which only data for a single arm met the inclusion criteria.
- No studies were identified that compared peginterferon alfa and RBV with BSC, nor peginterferon alfa-2a with peginterferon alfa-2b.
- On the whole, the cohort studies were relatively small and of generally poor quality.

Studienergebnisse:

Sustained virological response rates

- ranged from 53% to 66% in children treated with peginterferon alfa-2a
- ranged from 29% to 75% in those treated with peginterferon alfa-2b
  - two peginterferon alfa-2b studies at the extremes of this range had very small participant numbers (n = 7, n = 12) which may raise a question over the reliability of the data
  - If these two studies are excluded, the SVR for peginterferon alfa-2b ranged from 49% to 65%.
- In five studies (two peginterferon alfa-2a and three peginterferon alfa-2b), children with genotype 2 or 3 appeared to have higher SVR rates than those with genotype 1, and three studies (two peginterferon alfa-2a and one peginterferon alfa-2b) found that children with low viral load at baseline achieved higher SVR rates than those with high viral load.
- In two peginterferon alfa-2b studies, children who were treatment naive were more likely to achieve an SVR than those who had been previously treated.
- It should be noted that numbers of children in some of these subgroups were very small and none of the studies was statistically powered for subgroup analysis; therefore, results should be interpreted with caution.

Rates of non-response

- variable, ranging from 12% to 25% (two peginterferon alfa-2a studies) and 17% to 51% (three peginterferon alfa-2b studies)

relapse rate

- 17% reported by one peginterferon alfa-2a study and a range of 3–17% across four peginterferon alfa-2b studies

Adverse events

- not consistently reported across all the studies but generally appeared typical of those associated with peginterferon and RBV, and included flu-like symptoms, headache, gastrointestinal symptoms and anaemia
- incidence of dose discontinuation due to adverse events was relatively low and ranged from 3% to 7% (two peginterferon alfa-2a studies) and 1% to 10% (two peginterferon alfa-2b studies)
- rate of dose modifications was variable and inconsistently reported, usually anaemia and neutropenia

QoL and growth

- very limited data
  - In one peginterferon alfa-2a study, most children showed no clinical changes in any of the measures of QoL.
  - The impact on growth was often presented only in a brief narrative so no firm conclusions can be drawn.

Anmerkung/Fazit der Autoren

It was not considered appropriate to combine the studies in a meta-analysis primarily because of study design and poor study quality.

Treatment of children and young people with peginterferon (alfa-2a or -2b) and RBV may be an effective treatment. Results from the independent Markov model suggest that peginterferon (alfa-2a or -2b) in combination with RBV is more effective and has lower lifetime costs than BSC. However, the available evidence is of poor quality.

3.4 Leitlinien

Indolfi G et al., 2018 [5].

Hepatology Committee of European Society of Paediatric Gastroenterology, Hepatology and Nutrition

Treatment of Chronic Hepatitis C Virus Infection in Children: A Position Paper

Leitlinienziel

This position paper was developed to assist pediatricians and patients in the clinical decision-making of treating children with chronic HCV infection. Furthermore, it could assist policy makers in optimizing the development of new drugs for HCV-infected children.

Methodik

Grundlage der Leitlinie: europaweites Gremium mit Fachleuten aus Pädiatrie und Gastroenterologie (Patient*innenbeteiligung unklar), Art der Abfrage der Interessenerklärungen unklar, Ergebnisse dargestellt, Formulierung der klinischen Fragestellungen unklar, systematische Suche, Auswahl und Bewertung der Literatur, formales Konsensusverfahren angewendet, Begutachtungsverfahren nicht beschrieben

Recherche/Suchzeitraum:

- back to June 1, 2007 up to and through June 1, 2017

LoE

- High [A] Further research is unlikely to change confidence in the estimate of the clinical effect
- Moderate [B] Further research may change confidence in the estimate of the clinical effect
- Low [C] Further research is extremely likely to effect confidence on the estimate of clinical effect

GoR

- Strong [1] Factors influencing the strength of the recommendation included the quality of the evidence, presumed patient-important outcomes, and cost
- Weak [2] Variability in preferences and values, or more uncertainty. Recommendation is made with less certainty, higher cost, or resource consumption

Sonstige methodische Hinweise

- Verknüpfung zwischen Literatur und Empfehlung nur indirekt, GRADE-Tabellen liegen nicht vor.
- Indolfi G is investigator in a Gilead Sciences-sponsored clinical trial (ClinicalTrials.-gov identifier: NCT02175758). L.H. participated as subinvestigator in ABBVIE's sponsored study on Ombitasvir, Paritaprevir, Ritonavir, Dasabuvir (M14-748 EudraCT 2015-000111-41). The remaining authors report no conflicts of interest.

Current Treatment for Children

Table 2 shows the drugs currently approved by the EMA and the FDA for treatment of children with chronic HCV infection, including their indications, age-specific limitations, dosage, and routes of administration. The fixed-dose combination of ledipasvir/sofosbuvir and the combination of sofosbuvir and ribavirin have been approved by FDA and EMA in April and June to July 2017, respectively. These drugs can be used for treatment of adolescents (12–17 years) or children weighing more than 35 kg with chronic HCV genotype 1, 4, 5, and 6 and genotype 2 and 3 infections, respectively. Children younger than 12 years in the United States and Europe can be treated with the dual therapy of PEG IFN a-2a or -2b and ribavirin. Children with HCV genotypes 1 or 4 infection should be treated for 48 weeks, whereas the ones with genotypes 2 or 3 should be treated for 24 weeks (21,35–38).

TABLE 2. Drugs approved by the European Medicines Agency and the Food and Drug Administration for treatment of children with chronic hepatitis C virus infection (date: August 2017)

Drug	Age, yr	Genotype	Dosage	Route of administration
Interferon α-2b	3–18	1–6	6×10^6 IU/m^2 3 times a week	Subcutaneous
Pegylated interferon α-2a	5–18	1–6	100 μg/m^2 per week	Subcutaneous
Pegylated interferon α-2b	3–18	1–6	1.5 μg/kg per week	Subcutaneous
Ribavirin	1–18	1–6	15 mg/kg per day in 2 divided doses	Oral
Sofosbuvir	12–17	2, 3	400 mg/day	Oral
Ledipasvir/sofosbuvir	12–17	1, 4–6	90/400 mg/day	Oral

21. Indolfi G, Guido M, Azzari C, et al. Histopathology of hepatitis C in children, a systematic review: implications for treatment. Expert Rev Anti Infect Ther 2015;13:1225–35.
35. Wirth S, et al. Peginterferon alfa-2b plus ribavirin treatment in children and adolescents with chronic hepatitis C. Hepatology 2005;41:1013–8.
36. Jara P, et al. Efficacy and safety of peginterferonalpha2b and ribavirin combination therapy in children with chronic hepatitis C infection. Pediatr Infect Dis J 2008;27:142–8.
37. Sokal EM, et al. Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection in children and adolescents. J Hepatol 2010;52:827–31.
38. Wirth S, 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.

TABLE 3. Ongoing studies with direct-acting antivirals in children and adolescents with chronic hepatitis C virus infection (last update September 2017)

Combined regimens	Genotype	Identifier	Expected completion
Glecaprevir/pibrentasvir	1–6	NCT 03067129	May 2022
Ombitasvir/paritaprevir/ritonavir ± dasabuvir ± ribavirin	1, 4	NCT 02486406	Sept 2019
Sfosbuvir + daclatasvir	4	NCT 03080415	June 2018
Ledipasvir/sofosbuvir*	1, 4	NCT 02868242	April 2019
Ledipasvir/sofosbuvir ± ribavirin	1, 4, 5, 6	NCT 02249182	July 2018
Sofosbuvir + ribavirin	2, 3	NCT 02175758	April 2018
Sofosbuvir/velpatasvir	1–6	NCT 03022981	Dec 2019
Gratisovir + ribavirin	1–6	NCT 02985281	June 2018

Pegylated Interferon and Ribavirin

Eleven studies reporting on combined treatment with PEG IFN and ribavirin were included. Overall, the efficacy of this combination therapy was higher for children infected by HCV genotypes 2 and 3 (90%) than for those infected by genotypes 1 and 4 (48%). Relapse rate, independent from genotype and treatment duration, was 6%. Treatment discontinuation was reported in 17% of the children treated. Discontinuation due to severe adverse events occurred in 2%.

35. Wirth S, et al. Peginterferon alfa-2b plus ribavirin treatment in children and adolescents with chronic hepatitis C. Hepatology 2005;41:1013–8.
36. Jara P, et al. Efficacy and safety of peginterferonalpha2b and ribavirin combination therapy in children with chronic hepatitis C infection. Pediatr Infect Dis J 2008;27:142–8.
37. Sokal EM, et al. Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection in children and adolescents. J Hepatol 2010;52:827–31.
38. Wirth S, 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.
44. Al Ali J, et al. Pegylated interferon alfa-2b plus ribavirin for the treatment of chronic hepatitis C genotype 4 in adolescents. Ann Hepatol 2010;9:156–60.
45. El-Karaksy HM, et al. Effect of interleukin-10 gene promoter polymorphisms 1082 G/A and 592 C/A on response to therapy in children and adolescents with chronic hepatitis C virus infection. Hum Immunol 2016;77:1248–53.
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Direct-acting Antiviral

Two trials published as full-length articles and 3 as abstracts were included. The overall efficacy of the different DAAs combinations tested was high (98%). Relapse rate was low (0.7%) and no treatment discontinuation was reported.

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52. Wirth S, et al. Sofosbuvir and ribavirin in adolescents 12 to 17 years old with hepatitis c virus genotype 2 or 3 infection. Hepatology 2017;66:1102–10.
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55. El-Sayed M, et al. A pilot study for safety and efficacy of 12 weeks sofosbuvir plus daclatasvir with or without ribavirin in Egyptian adolescents with chronic hepatitis C virus Infection. J Hepatol 2017;66:THU412.

Patients Group 1: Treatment of Chronic Hepatitis C Virus Infection in Adolescents

Empfehlung 1 (C1)

IFN-free regimens are the best options in HCV-infected adolescents (>12 years of age, weight >35 kg) independently of the stage of liver disease and of comorbidities.

Empfehlung 2 (C1)

PEG IFN and ribavirin are presently no more recommended for treatment of HCV-infected adolescents since 2017.

Empfehlung 3 (C1) – Genotyp 1 oder 4

We recommend that children older than 12 years or who weigh >35 kg chronically infected with HCV genotype 1 or 4, are treated with the combination of ledipasvir (90 mg)/sofosbuvir (400 mg) with a single tablet administered once daily for 12 weeks.

Empfehlung 4 (C2) – Genotyp 1 oder 4

The recommended duration of therapy for treatment-experienced children with HCV genotype 1 infection and with compensated cirrhosis is 24 weeks.

Empfehlung 5 (C1) – Genotyp 2 oder 3

We recommend that children older than 12 years or who weigh >35 kg chronically infected with HCV genotype 2 are treated with sofosbuvir 400 mg once daily and weight-based ribavirin (15 mg/kg in 2 divided doses) for 12 weeks.

Empfehlung 6 (C1) – Genotyp 2 oder 3

We recommend that children older than 12 years or who weigh >35 kg chronically infected with HCV genotype 3 are treated with sofosbuvir 400 mg once daily and weight-based ribavirin (15 mg/kg in 2 divided doses) for 24 weeks.

Patients Group 2: Treatment of Chronic Hepatitis C Virus Infection in Children Younger Than 12 Years

No IFN-free treatment option is yet available for children younger than 12 years infected with HCV. There is uncertainty about how to manage these children. In the past, most of the children who received the therapy were treated independently of the stage of HCV-related liver damage to cure the infection and prevent the unpredictable progression of the disease. On the contrary, the majority of the infected children did not receive treatment given the overall mild nature of HCV-related liver disease, the low efficacy of PEG IFN with ribavirin (especially for

genotypes 1 and 4) and its burdensome safety profile. At present, the latter approach is even more justified, given the results of the DAAs combinations in older pediatric age cohorts and the preliminary results of the fixed-dose combination of ledipasvir/sofosbuvir in children aged 6 to 11 years (53). In this prospective, open-label, uncontrolled trial 90 patients had been enrolled and all were treated with ledipasvir (45 mg) and sofosbuvir 200mg once daily with a single tablet administered once daily for 12 weeks, except 1 genotype 1 treatment-experienced cirrhotic patient and 2 genotype 3 patients, who received 24 weeks of therapy. Eighty-six (96%) of the patients were infected by HCV genotype 1, and 2 each (2%) by HCV genotype 3 and 4. Eighteen (20%) were treatment-experienced and 2 had cirrhosis. Ninety-nine percent (89/90) of the children treated achieved SVR. One genotype 1a patient with cirrhosis relapsed at fourth follow-up visit. The most commonly reported adverse events were headache (19%), fever (17%), and abdominal pain (15%) (53).

In most cases treatment of children younger than 12 years could be postponed until the expected extension to the existing age indication for DAAs is granted. It is possible that the treatment could be warranted in isolated cases when there is a high clinical suspicion of advanced liver disease that is confirmed by a liver biopsy showing significant fibrosis (14,22,23,30). Such cases should be referred to a centre with experience in the treatment of children with chronic HCV infection and possible off-label use of DAAs should be considered.

14. 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;134:1900–7.
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23. Guido M, Bortolotti F, Leandro G, et al. Fibrosis in chronic hepatitis C acquired in infancy: is it only a matter of time? Am J Gastroenterol 2003;98:660–3.
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53. Murray KF, et al. Ledipasvir/sofosbuvir ribavirin for 12 or 24 weeks is safe and effective in children 6-11 years old with chronic hepatitis C infection. J Hepatol 2017;66:S101.

Empfehlung 1 (C1)

We no longer recommend PEG IFN and ribavirin as a general treatment for children younger than 12 years infected with HCV.

Empfehlung 2 (C1)

In children younger than 12 years the decision to initiate therapy should be individualized to isolated cases based on the HCV genotype, severity of liver disease (as assessed by liver biopsy), potential for side effects, likelihood of response and presence of comorbidities. These cases should be referred to a center with experience in the treatment of children with chronic HCV infection and the possible off-label use of DAAs could be considered.

American Association for the Study of Liver Diseases (AASLD), and Infectious Diseases Society of America (IDSA), 2017 [1].

HCV guidance: Recommendations for testing, managing, and treating Hepatitis C

Leitlinienziel

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: repräsentatives Gremium (Patient*innenbeteiligung unklar), Interessen einheitlich abgefragt und dargestellt, Umgang mit Interessenkonflikten erklärt, klinische Fragestellungen unklar, systematische Recherche, Auswahl und Bewertung der Literatur wahrscheinlich, Ableitung der Empfehlungen ohne formalisiertes Verfahren, internes Fachgruppenreview, permanente Aktualisierung

Recherche/Suchzeitraum:

- from 2010 to the present

LoE

- 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 favour 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.

GoR

- 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.

Sonstige methodische Hinweise

- Evidenz wird indirekt mit Empfehlung über den Hintergrundtext verknüpft.

Recommendations for Whom and When to Treat Among HCV-Infected Children

Empfehlung 1 (I, B)

If direct-acting antiviral (DAA) regimens are available for a child's age group, treatment is recommended for all HCV-infected children older than 3 years as they will benefit from antiviral therapy, independent of disease severity.

Empfehlung 2 (II, C)

Treatment of children aged 3 to 11 years with chronic hepatitis C should be deferred until interferon-free regimens are available.

Empfehlung 3 (I, C)

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.

Recommended regimens listed by evidence level and alphabetically for: Adolescents ≥12 Years Old or Weighing ≥35 kg, Without Cirrhosis or With Compensated Cirrhosis

Empfehlung 1 (I, B)

Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) for patients with genotype 1 who are treatment-naive without cirrhosis or with compensated cirrhosis[a], or treatment-experienced[b] without cirrhosis duration: 12 weeks

Empfehlung 2 (I, B)

Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) for patients with genotype 1 who are treatment-experienced[b] with compensated cirrhosis[a] duration: 24 weeks

Empfehlung 3 (I, B)

Daily sofosbuvir (400 mg) plus weight-based ribavirin[c] for patients with genotype 2 who are treatment-naive or treatment-experienced[b] without cirrhosis or with compensated cirrhosis[a] duration: 12 weeks

Empfehlung 4 (I, B)

Daily sofosbuvir (400 mg) plus weight-based ribavirin[c] for patients with genotype 3 who are treatment-naive or treatment-experienced[b] without cirrhosis or with compensated cirrhosis[a] duration: 24 weeks

Empfehlung 5 (I, B)

Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) for patients with genotype 4, 5, or 6 who are treatment-naive or treatment-experienced[b] without cirrhosis or with compensated cirrhosis[a] duration: 12 weeks

[a] Child-Pugh A

[b] Patients who have failed an interferon-based regimen, with or without ribavirin

[c] See ribavirin dosing table for recommended weight-based dosages.

Balistreri WF, et al. The safety and effectiveness of ledipasvir-sofosbuvir in adolescents 12-17 years old with hepatitis C virus genotype 1 infection. Hepatology (Baltimore, Md.). 2017;66(2):371 - 378.
Wirth S, et al. Sofosbuvir and ribavirin in adolescents 12-17 years old with hepatitis C virus genotype 2 or 3 infection. Hepatology (Baltimore, Md.). 2017;.

Sarrazin C et al., 2018 [6,7] und Zimmermann T et al., 2018 [9].

AWMF-Leitlinie; Deutsche Gesellschaft für Gastroenterologie, Verdauungs- und Stoffwechselkrankheiten (DGVS)

S3-Leitlinie "Prophylaxe, Diagnostik und Therapie der Hepatitis-C-Virus (HCV) -Infektion"

Methodik

Grundlage der Leitlinie: Aktualisierung der Vorversion, repräsentatives Gremium (inklusive Patient*innen), Interessen einheitlich abgefragt und dargelegt, Umgang mit Interessenkonflikten erklärt, klinische Fragestellungen formuliert, systematische Recherche, Auswahl und Bewertung der Literatur, Ableitung der Empfehlungen mit formalisierten

Verfahren, externe Begutachtung und Verabschiedung durch die Vorstände der herausgebenden Fachgesellschaften und Organisationen

Recherche/Suchzeitraum:

- Keine neue Recherche für den Abschnitt Kinder und Jugendliche. Der Recherchezeitraum wurde in der alten Leitlinie von 2010 nicht angegeben. Die Leitlinien-Erstellung der Leitlinie von 2010 wurde am 12.11.2007 begonnen und am 7.9.2009 formal abgeschlossen.

LoE

Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence

Question	Step 1 (Level 1*)	Step 2 (Level 2*)	Step 3 (Level 3*)	Step 4 (Level 4*)	Step 5 (Level 5)
How common is the problem?	Local and current random sample surveys (or censuses)	Systematic review of surveys that allow matching to local circumstances**	Local non-random sample**	Case-series**	n/a
Is this diagnostic or monitoring test accurate? (Diagnosis)	Systematic review of cross sectional studies with consistently applied reference standard and blinding	Individual cross sectional studies with consistently applied reference standard and blinding	Non-consecutive studies, or studies without consistently applied reference standards**	Case-control studies, or "poor or non-independent reference standard**	Mechanism-based reasoning
What will happen if we do not add a therapy? (Prognosis)	Systematic review of inception cohort studies	Inception cohort studies	Cohort study or control arm of randomized trial*	Case-series or case-control studies, or poor quality prognostic cohort study**	n/a
Does this intervention help? (Treatment Benefits)	Systematic review of randomized trials or *n*-of-1 trials	Randomized trial or observational study with dramatic effect	Non-randomized controlled cohort/follow-up study**	Case-series, case-control studies, or historically controlled studies**	Mechanism-based reasoning

GoR

Formulierung	Evidenzgrad	Empfehlungsgrad	Empfehlungsstärke
soll	I	A	starke Empfehlung
sollte	II	B	Empfehlung
kann	III und schlechter	0	Empfehlung offen

Der Evidenzgrad kann vom Empfehlungsgrad abweichen (das heißt eine A-Empfehlung bei Evidenzgrad II oder umgekehrt). Gründe wären zum Beispiel Inkonsistenz der Studienergebnisse, klinische Relevanz der Endpunkte und Effektstärken, Nutzen-Risiko-Verhältnis, Patientenpräferenz etc. und sollten dann angegeben werden. Bei fehlender Evidenz wurde die Empfehlung als Expertenkonsens (EK) klassifiziert.

Sonstige methodische Hinweise

- Nach einer orientierenden Literaturrecherche für die AG 7 „Hepatitis C-Virusinfektion bei Kindern und Jugendlichen“ konnte keine neue oder höhere Evidenz identifiziert werden. Die Empfehlungen der alten Leitlinie wurden unverändert aus der alten Leitlinie übernommen.
- Die Verwendung von Evidenz- und Empfehlungsgraden ist unklar. Dargestellt werden Evidenzgrade. Diese entsprechen nicht dem angegebenen Oxford-Schema (siehe LoE oben).
- Evidenz wird indirekt mit Empfehlung über den Hintergrundtext verknüpft.

Therapieoptionen und Therapieziele im Kindesalter

EMPFEHLUNG 7.2.1

Die Therapie der Hepatitis C im Kindes- und Jugendalter orientiert sich an den Empfehlungen im Erwachsenenalter.
Das Therapieziel bei der Behandlung der chronischen Hepatitis C bei Kindern und Jugendlichen ist die Viruselimination mit Negativierung der HCV-RNA im Serum und damit Ausheilung der Erkrankung (I). #
Eine akute Hepatitis C im Kindes- und Jugendalter sollte wie bei Erwachsenen behandelt werden (EK). #
 # Konsensstärke: 96 %, starker Konsens*

Für eine antivirale Therapie der akuten Hepatitis C liegen für die Altersgruppe keine Daten vor. Da von einer hohen Chronifizierungsrate ausgegangen werden muss, sollte wie bei Erwachsenen vorgegangen werden.

Die Behandlung kann aufgrund der Zulassungsbestimmungen frühestens ab dem vollendeten dritten Lebensjahr begonnen werden. Dies steht einerseits im Zusammenhang mit dem Profil der unerwünschten Wirkungen und andererseits mit der Tatsache, dass bis zu diesem Alter eine gewisse Chance auf eine spontane Viruselimination besteht. Bisherige Erfahrungen zeigen, dass die Rückfall-Rate bei erfolgreich behandelten Kindern mit einer persistierend negativen HCV-RNA über 6 Monate nach Abschluss der Behandlung extrem niedrig ist (Ib) [694, 705].

Die Kombinationstherapie aus Paritaprevir/r, Ombitasvir und Dasabuvir wurde bei 12- bis 17-jährigen Patienten untersucht [706]. Das Kombinationspräparat aus Ledipasvir 90 mg/Sofosbuvir 400mg ist für 12- bis 17-Jährige mit einem Körpergewicht von über 45 kg zugelassen. Bei Kindern im Alter von 6 bis 11 Jahren wurde in einer Phase-2-Studie die Gabe des Kombinationspräparats aus Ledipasvir 45mg und Sofosbuvir 200mg einmal täglich untersucht [707]. Hierbei zeigten sich SVR-Raten von 99 Prozent (n = 89/90). Genotyp-1-Patienten wurden über 12 Wochen therapiert (n = 85). Genotyp-3- Patienten (n = 2) erhielten Sofosbuvir/Ledipasvir plus Ribavirin über 24 Wochen. Die häufigsten Nebenwirkungen waren abdominelle Beschwerden, Kopfschmerzen, Müdigkeit, Pyrexie, Husten und oropharyngeale Schmerzen. Bei keinem der Patienten wurde die Therapie abgebrochen. Weitere Studien bei 3- bis 5-Jährigen laufen. Für Jugendliche im Alter von 12 bis <18 Jahren mit HCV-Genotyp 2 und 3 ist derzeit Sofosbuvir und Ribavirin zugelassen.

[694] Bortolotti F, Iorio R, Nebbia G et al. Interferon treatment in children with chronic hepatitis C: long-lasting remission in responders, and risk for disease progression in non-responders. Digestive and liver disease : official journal of the Italian Society of Gastroenterology and the Italian Association for the Study of the Liver 2005; 37: 336–341
[701]. Wirth S, et al. Peginterferon alfa-2b plus ribavirin treatment in children and adolescents with chronic hepatitis C. Hepatology 2005; 41: 33 1013-1018
[702]. Wirth S, et al. High sustained virologic response rates in children with chronic hepatitis C receiving peginterferon alfa-2b plus ribavirin. J Hepatol 2010; 52: 501-507
[705] Kelly DA, Haber B, Gonzalez-Peralta RP et al. Durability of sustained response shown in paediatric patients with chronic hepatitis C who were treated with interferon alfa-2b plus ribavirin. Journal of viral hepatitis 2012; 19: 263–270
[706] Leung DH, Yao B, Viani RM et al. ZIRCON: pharmacokinetics, safety, and efficacy of ombitasvir/paritaprevir/ritonavir +/- dasabuvir +/- ribavirin in adolescents with genotype 1 or 4 hepatitis C virus infection. Journal of hepatology 2017; 66: S300–S301
[707] Murray KF, Balistreri W, Bansal S et al. Ledipasvir/sofosbuvir +/- ribavirin for 12 or 24 weeks is safe and effective in children 6–11 years old with chronic hepatitis C infection. Journal of hepatology 2017; 66: S57–S58

World Health Organization (WHO), 2018 [8].

Guidelines for the screening, care and treatment of persons with chronic hepatitis C infection

Methodik

Grundlage der Leitlinie: Aktualisierung der Version von 2016, internationales multidisziplinäres Gremium (Patient*innenbeteiligung unklar), Interessen einheitlich abgefragt und dargestellt, klinische Fragestellungen im PICO-Format formuliert, systematische Recherche, Auswahl und Bewertung (GRADE) der Literatur, Ableitung der Empfehlungen mit standardisiertem GRADE-Verfahren, externe Begutachtung

Recherche/Suchzeitraum:

- from 1994 to the present

LoE (GRADE categories of quality of evidence)

- High: we are very confident that the true effect lies close to that of the estimate of the effect.
- Moderate: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
- Low: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
- Very low: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of the effect.

GoR

- We recommend against the option
- We suggest considering the option
  - Only in the context of rigorous research
  - Only with targeted monitoring and evaluation
  - Only in specific contexts
- We recommend the option

Treatment of adolescents (12–17 years) and deferral of treatment in children (<12 years of age)

In adolescents aged 12–17 years or weighing at least 35 kg with chronic HCV,* WHO recommends:

- **sofosbuvir/ledipasvir for 12 weeks** in genotypes 1, 4, 5 and 6** *(strong recommendation, very low quality of evidence)*
- **sofosbuvir/ribavirin for 12 weeks in genotype 2** *(strong recommendation, very low quality of evidence)*
- **sofosbuvir/ribavirin for 24 weeks in genotype 3** *(strong recommendation, very low quality of evidence).*

* In those without cirrhosis or with only compensated cirrhosis

** Treatment for 24 weeks in those who are treatment experienced and with compensated cirrhosis

In children aged less than 12 years with chronic hepatitis C,* WHO recommends:

- **deferring treatment until 12 years of age**** *(conditional recommendation, low quality of evidence)*
- **treatment with interferon-based regimens should no longer be used*** *(strong recommendation, very low quality of evidence).*

* In those without cirrhosis or with only compensated cirrhosis

**Prior to approval of DAAs for children aged <12 years of age, exceptional treatment with interferon + ribavirin may be considered for children with genotype 2 or 3 infection and severe liver disease. This may include children at higher risk of progressive disease, such as with HIV coinfection, thalassaemia major and survivors of childhood cancer.

Prior to regulatory approval of DAA's for use in children, the standard of care of adolescents and children infected with HCV was dual therapy with pegylatedinterferon and ribavirin for 24 weeks for genotypes 2 and 3, and 48 weeks for genotypes 1 and 4 (109–117). This combination resulted in an SVR rate of around 52% in children infected with HCV genotypes 1 and 4, and 89% in those infected with HCV genotypes 2 and 3 (109, 110, 112, 114), but was associated with significant side-effects.

In 2017, two DAA regimens (sofosbuvir/ledipasvir and sofobuvir/ribavirin) received regulatory approval from FDA and EMA for use in adolescents (≥12 years) (118, 119). Trials are ongoing to evaluate pangenotypic DAA regimens in both adolescents (≥12 years) and children (aged 6–11 years). As of June 2018, in those younger than 12 years, the only licensed treatment options remain interferon with ribavirin as DAAs are not yet approved for use in younger children, and the Guidelines Development Group therefore formulated separate recommendations for adolescents and children. None of the recommended pangenotypic DAAs in these current guidelines (sofosbuvir/daclatasvir or sofosbuvir/velpatasvir) are yet approved for use in either adolescents and children, but this is anticipated in 2019, which would represent a major opportunity to advance treatment access (120, 121).

The main evidence base to support treatment recommendations in adolescents aged 12 or more years were the two studies used for regulatory approval of the regimens (118, 119), and the extensive evidence base from DAA trials in adults.

Summary of the evidence

Adolescents (12–17 years)

The regulatory approval by the FDA and EMA in April and June 2017, respectively, of the use of a fixed-dose combination of sofosbuvir/ledipasvir for genotype 1-infected adolescents aged 12–17 years old or weighing ≥35 kg, and sofosbuvir/ ribavirin for those infected with HCV genotype 2 or 3 was based on the extensive data in adults of high rates of cure and low rates of toxicity, and two studies of pharmacokinetics, efficacy and safety in adolescents (118, 119). In one study, 100 genotype 1 HCV-infected treatment-naive and -experienced adolescents were treated with sofosbuvir/ledispasvir as a single tablet once daily for 12 weeks (118). The SVR was 98% with good tolerability. A second study evaluated the use of sofosbuvir and weight-based ribavirin for 12 weeks in 52 adolescents with genotype 2 or 3 infection (119). SVR rates were 100% (13/13) in genotype 2 and 97% (38/39) in persons with genotype 3. No

serious adverse effects leading to treatment discontinuation or significant abnormalities in laboratory results were reported. This study also reported an improvement in health-related quality of life following SVR (122), particularly in social functioning and school performance domains.

Children (6–12 years)

Currently, the only licensed, approved treatment option for children younger than 12 years is pegylated-interferon α-2a or -2b injections with twice-daily ribavirin tablets, for 24 to 48 weeks depending on the HCV genotype (109–117). In genotype 1, the SVR of pegylated-interferon/ribavirin is suboptimal compared to DAAs; and only 52% in those with HCV genotype 1 and 4, but 89% in genotypes 2 and 3 (109–111, 114). Pegylated-interferon and ribavirin are associated with significant side-effects, and potentially irreversible post-therapy side-effects, such as thyroid disease, type 1 diabetes, ophthalmological complications and growth impairment (112, 114, 123–127). None of the DAAs are approved yet for use in children aged less than 12 years. There are two ongoing studies of half-dose sofosbuvir/ledipasvir in 90 treatment-naive or -experienced children aged 6 to 12 years infected with HCV genotypes 1, 3 and 4, and sofosbuvir plus ribavirin in children aged 6 to 12 years (120).

Rationale for the recommendations

Treat adolescents ≥12 years or weighing at least 35 kg (without cirrhosis or with only compensated cirrhosis) with sofosbuvir/ledipasvir and sofosbuvir/ribavirin

The Guidelines Development Group recommended that all chronically HCV infected adolescents should be offered treatment with the current FDA- and EMA approved regimens of sofosbuvir/ledipasvir and sofosbuvir/ribavirin. Data on DAA therapy in HCV-infected adolescents is limited. The recommendation was based on both indirect evidence from adult treatment studies and two published trials in adolescents (118, 119) of specific recommended regimens (sofosbuvir/ledipasvir and sofosbuvir/ribavirin) used for regulatory approval by the EMA and FDA that showed high efficacy and safety rates and pharmacokinetic equivalence. A systematic review and metaanalysis comparing DAAs with pegylated-interferon in adolescents (128) also confirmed higher efficacy and tolerability of oral short-course DAA treatments when compared to interferon therapy in adolescents and children.This recommendation was therefore strong despite the low quality of evidence specific to adolescents.

The Guidelines Development Group recognized that the recommended regimens had limitations.

1. These regimens are not pangenotypic and therefore genotyping will still be required. Pangenotypic DAA regimens would be preferable in settings with a range of genoptypes. DAAs under evaluation in adolescents include sofosbuvir/velpatasvir, sofosbuvir/daclatasvir and glecaprevir/pibrentasvir.

2. There remains limited data on treatment in those with cirrhosis, but recommendations include those with compensated cirrhosis. In those who are treatment experienced and with compensated cirrhosis, treatment for 24 weeks is recommended.

3. Use of a ribavirin-based regimen requires haematological monitoring. Ribavirin is also teratogenic and contraindicated in pregnancy. This is important as adolescents are more likely to have unplanned pregnancies. Extreme care must be taken to avoid pregnancy during

therapy and for 6 months after completion of therapy, as well as in partners of HCV-infected men who are taking ribavirin therapy.

4. Sofosbuvir with ribavirin is a suboptimal regimen for persons with genotype 3 infection, especially if they have cirrhosis. The Guidelines Development Group noted that the EMA indicates that sofosbuvir/ledipasvir can be considered for use in some persons infected with genotype 3, and so a potential off-label use of sofosbuvir/ledipasvir plus ribavirin is a possible option for adolescents with genotype 3 HCV infection.

Deferral of treatment in children until 12 years

In children less than 12 years, the Guidelines Development Group recommended that treatment be deferred until they either reach 12 years or until DAA regimens are approved for those less than 12 years. Interferon-based regimens should no longer be used for either adolescents or children (except in situations where there is no alternative). The Guidelines Development Group recognized that the benefits of deferral far outweigh the small risk of progression of liver fibrosis during childhood, and the unpredictable rapid development of advanced liver disease in a few children (83, 129).

The key reasons for the current conditional recommendation to defer HCV treatment in children aged less than 12 years were as follows:

- 1. The low frequency of HCV-related liver disease in childhood. Only a small number of children experience significant morbidity that would benefit from early treatment.
- 2. The only available and approved regimen for this age group is pegylatedinterferon/ ribavirin. This regimen has an overall low efficacy, a prolonged treatment duration (6–12 months), an inconvenient administration route (via injection), significant side-effects and high costs.
- 3. New, highly effective short-course oral pangenotypic DAA regimens are likely to become available for children <12 years in 2019.

Treatment with interferon should not be used

The key reasons for the current strong recommendation that interferon should not be used in children aged less than 12 years despite the very low quality of evidence were as follows:

- The issues with interferon-containing regimens and ribavirin in children. These include long duration of treatment, limited efficacy and burdensome side-effects, including high rates of flu-like symptoms and haematological complications (anaemia, leukopenia and neutropenia), and several potentially irreversible side-effects, such as thyroid disease, type 1 diabetes, ophthalmological complications and impaired growth (112, 114, 123–127).
- 2. The imminent arrival of alternative DAA options. Preliminary trial data show much higher efficacy and safety of DAAs in children less than 12 years compared to interferon, as observed for adults and adolescents.
- 3. The low availability of interferon. Interferon is increasingly less available, especially in LMICs. It requires a cold chain, which makes delivery to scale less feasible.

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4 Detaillierte Darstellung der Recherchestrategie

Cochrane Library - Cochrane Database of Systematic Reviews (Issue 6 of 12, June 2019) am 05.06.2019

#	Suchfrage
1	MeSH descriptor: [Hepatitis C, Chronic] explode all trees
2	(chronic and (hepatitis NEAR/3 c)):ti,ab,kw
3	(HCV):ti,ab,kw
4	#1 OR #2 OR #3
5	#4 with Cochrane Library publication date from Jun 2014 to Jun 2019, in Cochrane Reviews

Systematic Reviews in Medline (PubMed) am 06.06.2019

#	Suchfrage
1	"hepatitis c, chronic"[mh]
2	((((chronic[Tiab]) AND hepatitis[Tiab]) AND c[Tiab])) OR (hcv[Ti])
3	(#1 OR #2)
4	(#3) AND (((Meta-Analysis[ptyp] OR systematic[sb] OR ((systematic review [ti] OR meta-analysis [pt] OR meta-analysis [ti] OR systematic literature review [ti] OR this systematic review [tw] OR pooling project [tw] OR (systematic review [tiab] AND review [pt]) OR meta synthesis [ti] OR meta-analy*[ti] OR integrative review [tw] OR integrative research review [tw] OR rapid review [tw] OR umbrella review [tw] OR consensus development conference [pt] OR practice guideline [pt] OR drug class reviews [ti] OR cochrane database syst rev [ta] OR acp journal club [ta] OR health technol assess [ta] OR evid rep technol assess summ [ta] OR jbi database system rev implement rep [ta]) OR (clinical guideline [tw] AND management [tw]) OR ((evidence based[ti] OR evidence-based medicine [mh] OR best practice* [ti] OR evidence synthesis [tiab]) AND (review [pt] OR diseases category[mh] OR behavior and behavior mechanisms [mh] OR therapeutics [mh] OR evaluation studies[pt] OR validation studies[pt] OR guideline [pt] OR pmcbook)) OR ((systematic [tw] OR systematically [tw] OR critical [tiab] OR (study selection [tw]) OR (predetermined [tw] OR inclusion [tw] AND criteri* [tw]) OR exclusion criteri* [tw] OR main outcome measures [tw] OR standard of care [tw] OR standards of care [tw]) AND (survey [tiab] OR surveys [tiab] OR overview* [tw] OR review [tiab] OR reviews [tiab] OR search* [tw] OR handsearch [tw] OR analysis [ti] OR critique [tiab] OR appraisal [tw] OR (reduction [tw]AND (risk [mh] OR risk [tw]) AND (death OR recurrence))) AND (literature [tiab] OR articles [tiab] OR publications [tiab] OR publication [tiab] OR bibliography [tiab] OR bibliographies [tiab] OR published [tiab] OR pooled data [tw] OR unpublished [tw] OR citation [tw] OR citations [tw] OR database [tiab] OR internet [tiab] OR textbooks [tiab] OR references [tw] OR scales [tw] OR papers [tw] OR datasets [tw] OR trials [tiab] OR meta-analy* [tw] OR (clinical [tiab] AND studies [tiab]) OR treatment outcome [mh] OR treatment outcome [tw] OR pmcbook)) NOT (letter [pt] OR newspaper article [pt])) OR Technical Report[ptyp]) OR (((((trials[tiab] OR studies[tiab] OR database*[tiab] OR literature[tiab] OR publication*[tiab] OR Medline[tiab] OR Embase[tiab] OR Cochrane[tiab] OR Pubmed[tiab])) AND systematic*[tiab] AND (search*[tiab] OR research*[tiab]))) OR ((((((((((HTA[tiab]) OR technology assessment*[tiab]) OR technology report*[tiab]) OR (systematic*[tiab] AND review*[tiab])) OR (systematic*[tiab] AND overview*[tiab])) OR meta-analy*[tiab]) OR (meta[tiab] AND analyz*[tiab])) OR (meta[tiab] AND analys*[tiab])) OR (meta[tiab] AND analyt*[tiab]))) OR (((review*[tiab]) OR overview*[tiab]) AND ((evidence[tiab]) AND based[tiab]))))))
5	(#4) AND ("2014/06/01"[PDAT] : "3000"[PDAT])
6	(#5) NOT retracted publication[ptyp]

Leitlinien in Medline (PubMed) am 06.06.2019

#	Suchfrage
1	"hepatitis c"[Majr]
2	("hepatitis c"[ti) OR HCV[ti]
3	(#1 OR #2)
4	(#3) AND ((Guideline[ptyp] OR Practice Guideline[ptyp] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp]) OR ((guideline*[ti] OR recommendation*[ti]) NOT (letter[ptyp] OR comment[ptyp])))
5	(#4) AND ("2014/06/01"[PDAT] : "3000"[PDAT])
6	(#5) NOT retracted publication[ptyp]

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