Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

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

Vorgang: 2017-08-15-D-304 Ledipasvir/Sofosbuvir (neues Anwendungsgebiet: - jugendliche Patienten (12-17 Jahre))

Stand: August 2017

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

Ledipasvir/Sofosbuvir
[chronische Hepatitis C bei Patienten zwischen 12 und <18 Jahren]

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 Tabelle 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	Keine Beschlüsse im Anwendungsgebiet für diese Patientengruppe.
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®	Behandlung der chronischen Hepatitis C (CHC) Infektion bei Jugendlichen im Alter von 12 bis < 18 Jahren.
Ribavirin J05AB04 Copegus®	Copegus wird in Kombination mit anderen Arzneimitteln zur Behandlung von chronischer Hepatitis C (CHC) angewendet. Beachten Sie auch die Fachinformationen der Arzneimittel, die in Kombination mit Copegus zur Behandlung von Hepatitis C angewendet werden. *Anwendung bei Patienten unter 18 Jahren:* Copegus wird nicht empfohlen für die Anwendung bei Kindern und Jugendlichen (< 18 Jahren) aufgrund nicht ausreichender Daten zur Unbedenklichkeit und Wirksamkeit in Kombination mit anderen Arzneimitteln zur Behandlung von Hepatitis C. Bei Kindern und Jugendlichen (6 – 18 Jahre) liegen nur begrenzte Daten zur Unbedenklichkeit und Wirksamkeit in Kombination mit Peginterferon alfa-2a vor. Hinsichtlich der Anwendung von Copegus bei Kindern ist eine Nutzen-Risiko-Bewertung in jedem Einzelfall erforderlich (siehe Abschnitt 4.4). *Behandlungsdauer* Die Behandlungsdauer ist abhängig von den Arzneimitteln, die in Kombination mit Copegus angewendet werden und kann zudem von verschiedenen Eigenschaften der Patienten oder des Virus abhängen, einschließlich Genotyp, Koinfektionen, Vorgeschichte der Behandlung und Ansprechen auf die Behandlung.
Ribavirin J05AB04 Rebetol®	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). *Kinder und Jugendliche (Kinder ab 3 Jahren und Jugendliche):* Rebetol kann in Kombination mit Peginterferon alfa-2b oder Interferon alfa-2b angewendet werden (siehe Abschnitt 4.4). Rebetol muss in einer Kombinationstherapie angewendet werden, wie in Abschnitt 4.1 beschrieben. Die entsprechenden Fachinformationen der Arzneimittel, die in Kombination mit Rebetol angewendet werden, sind für zusätzliche Informationen zur Verschreibung dieser Arzneimittel und für weitere Dosierungsempfehlungen bei gleichzeitiger Gabe mit Rebetol zu beachten.

II. Zugelassene Arzneimittel im Anwendungsgebiet

Interferon alfa-2b L03AB05 Intron-A®	*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. *Behandlungsdauer bei Kindern und Jugendlichen* • *Genotyp 1:* Die empfohlene Behandlungsdauer beträgt 1 Jahr. Es ist sehr unwahrscheinlich, dass Patienten, die nach 12 Wochen Behandlung kein virologisches Ansprechen zeigten (negativer Vorhersagewert 96 %), doch noch ein anhaltendes virologisches Ansprechen zeigen. Aus diesem Grund wird empfohlen, die Kombinationstherapie mit IntronA 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 2/3:* Die empfohlene Behandlungsdauer beträgt 24 Wochen.
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). 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.

II. Zugelassene Arzneimittel im Anwendungsgebiet

Peginterferon alfa-2a L03AB11 Pegasys®	*Pädiatrische Patienten ab 5 Jahren:* Pegasys ist in Kombination mit Ribavirin zur Behandlung von Kindern und Jugendlichen ab 5 Jahren mit bisher noch nicht behandelter chronischer Hepatitis C, 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). *Dauer der Behandlung* Bei Kindern und Jugendlichen mit chronischer Hepatitis C ist die Dauer der Behandlung mit Pegasys in Kombination mit Ribavirin vom viralen Genotyp abhängig. Patienten, die mit den viralen Genotypen 2 oder 3 infiziert sind, sollen eine Behandlung über 24 Wochen erhalten und Patienten, die mit einem anderen Genotyp infiziert sind, sollen eine Behandlung über 48 Wochen erhalten.

Quellen: Fachinformationen, Stand 08/2017.

Gemeinsamer Bundesausschuss

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie (zVT):

Inhalt

Systematische Recherche:

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen, HTA-Berichten und Evidenz-basierten systematischen Leitlinien zur Indikation *Chronische Hepatits C Infektion* durchgeführt. Der Suchzeitraum wurde auf die letzten 5 Jahre eingeschränkt und die Recherche am 30.11.2016 abgeschlossen. Die Suche erfolgte in folgenden Datenbanken bzw. Internetseiten folgender Organisationen: The Cochrane Library (Cochrane Database of Systematic Reviews, Health Technology Assessment Database), MEDLINE (PubMed), AWMF, Clinical Evidence, DAHTA, G-BA, GIN, IQWiG, NGC, 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 1238 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 5 Quellen, die in die synoptische Evidenz-Übersicht aufgenommen wurden.

Indikation:

Chronische Hepatits C (alle Genotypen) bei Adoleszenten zwischen 12 und <18 Jahren.

Abkürzungen:

AE	Adverse event
Akdae	Arzneimittelkommission der deutschen Ärzteschaft
ÄZQ	Ärztliches Zentrum für Qualität in der Medizin
AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
BSC	Best supportive care
CCO	Cancer Care Ontario
CHC	Chronic hepatitis C
DAA	Direct-acting antiviral agent
DAHTA	Deutsche Agentur für Health Technology Assessment
DRKS	Deutsches Register Klinischer Studien
ESMO	European Society for Medical Oncology
G-BA	Gemeinsamer Bundesausschuss
GIN	Guidelines International Network
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
HRQoL	Health-Related Quality of Life
ICTRP	International Clinical Trials Registry Platform
INF	interferon
ISRCTN	International Standard Randomised Controlled Trial Number
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
NGC	National Guideline Clearinghouse
NHS CRD	National Health Services Center for Reviews and Dissemination
NICE	National Institute for Health and Care Excellence
RBV	Ribavirin
SIGN	Scottish Intercollegiate Guidelines Network
SVR	Sustained virological response
TRIP	Turn Research into Practice Database
WHO	World Health Organization

IQWiG Berichte/G-BA Beschlüsse

Bislang liegen keine IQWiG-Berichte oder G-BA Beschlüsse vor.

Cochrane Reviews

Es konnten keine Cochrane Reviews identifiziert werden.

Systematische Reviews

Hartwell D et al., 2014 [1]. **NHS National Institute for Health Research** 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	1. Fragestellung To assess the clinical effectiveness and cost-effectiveness of peginterferon alfa-2a and peginterferon alfa-2b in combination with ribavirin (RBV), within their licensed indications, for the treatment of chronic hepatitis C virus (HCV) in children and young people aged 3–17 years
	Methodik Population: Children and young people aged 3–17 years (peginterferon alfa-2b) or 5–17 years (peginterferon alfa-2a) with chronic HCV, without liver decompensation and who were positive for HCV RNA. All groups were considered, including: 1. people with HIV co-infection; 2. people with all grades of severity of chronic hepatitis C (mild, moderate and severe); 3. people who were treatment naive or, if appropriate, those who had been previously treated but who relapsed or did not respond. Intervention: • Peginterferon alfa-2a in combination with RBV or • 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. Endpunkte: • SVR (defined as undetectable HCV RNA at least 6 months after treatment cessation). • Studies could also include one or more of the following: o virological response to treatment (e.g. during treatment, end of treatment) o biochemical response (e.g. ALT) o liver inflammation and fibrosis

	o mortality o adverse effects of treatment, including effects on growth o HRQoL Suchzeitraum (Aktualität der Recherche): 12 electronic bibliographic databases (including The Cochrane Library, MEDLINE and EMBASE) from database inception to November 2012. Bibliographies of retrieved papers were screened, general and key hepatitis C websites and symposia were searched, and experts were also contacted to identify any additional published and unpublished references. Manufacturers' submissions (MSs) to NICE were also searched Anzahl eingeschlossene Studien/Patienten (Gesamt): 7 studies reported in 15 publications Evidenzbasis: Randomised controlled trials (RCTs) and non-RCTs were eligible for inclusion; uncontrolled studies were considered in the absence of any controlled studies Qualitätsbewertung der Studien: CRD (University of York). Centre for Reviews and Dissemination (CRD). Systematic Reviews: CRD's Guidance for Undertaking Reviews in Health Care. 3rd edn. York: York Publishing Services Ltd; 2009 Results were robust to changes in the sensitivity analyses.
	3. Ergebnisdarstellung <u>Studiencharakteristika</u> • Seven studies (two peginterferon alfa-2a and five peginterferon alfa-2b) were included; six were single-arm, uncontrolled cohort studies and one was a RCT for which only data for a single arm met the inclusion criteria. • Severity of chronic HCV Mild fibrosis (most or all of the population), n = 6; unclear, n = 1.; HIV co-infection n = 0. • Treatment: Peginterferon alfa-2a/-2b Peginterferon alfa-2a, n = 2; peginterferon alfa-2b, n = 5. • Treatment naive/previously treated Treatment naive (100% of population), n = 4; mixed treatment (naive and previously treated), n = 2; unclear, n = 1. • Five of the studies (both peginterferon alfa-2a,56,57 three peginterferon alfa-2b48,51,59) included participants with a mix of genotypes, although all included a higher proportion of participants with genotype 1 (range 50–87%), or genotypes 1 or 4 (range 71–96%) than the other genotype subgroups. Participants with genotypes 2 or 3 accounted for only 3–25% of the included populations across the studies. • Studies differed in the numbers of centres and countries that they included. • Rekrutierung fand statt in Ägypten, Kuweit, Südamerika (u.a. Brasilien) und Europa (UK, Belgien, Lettland, Schweden) <u>Qualität der Studien</u> • On the whole, the cohort studies were of generally poor quality, although the study by Schwarz and colleagues56 (peginterferon alfa-

2a) fared better in its reporting of methodological details.

- The studies were relatively small (range 7–107 participants) and of generally poor quality, with a potentially high risk of bias (owing to the study design) and little reporting of data/statistical analysis. Therefore, caution is advised in the interpretation of results.
- The generalisability of the studies to a UK population of children and young people is uncertain

TABLE 3 Assessment of study quality

Quality criteria	Schwarz et al., 2011[56]	Sokal et al., 2010[57]	Wirth et al., 2010[59]	Pawlowska et al., 2010[51]	Al Ali et al., 2010[46]	Ghaffar et al., 2009[47]	Jara et al., 2008[48]
Selection criteria predefined	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Blinding of participants	Yes	N/A	N/A	N/A	N/A	N/A	N/A
More outcomes measured than reported	Yes	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Withdrawals and dropouts described	Yes[a]	Yes	Yes	NR	Yes	NR	Yes
Analysis accounts for missing data	Unclear	Unclear	Unclear	No	Unclear	N/A[b]	No
If analysis accounts for missing data, were methods appropriate?	N/A	N/A	N/A	N/A	N/A	N/A	N/A

N/A, not applicable; NR, not reported.
a Numbers, timing and reasons for dropouts reported but unclear whether or not four patients who discontinued the drug were classified as dropouts.
b No analysis conducted.

- Schwarz et al, 2011: RCT doppelblind: placebo or RBV in combination with peginterferon alfa-2a
- Andere Studien: unkontrollierte Kohortenstudien

Ergebnisse

<u>Sustained virological Response</u>

	• Sustained virological response rates ranged from 53% to 66% for peginterferon alfa-2a and 29% to 75% for peginterferon alfa-2b. (detaillierte Darstellung siehe Anhang) • For both peginterferon alfa-2a and peginterferon alfa-2b, children with genotype 2 or 3 appeared to have higher SVR rates than those with genotype 1, and children with low viral load at baseline achieved higher SVR rates than those with high viral load in three studies • Where participants were of mixed treatment history children who were treatment naive were more likely to achieve a SVR than those who had been previously treated. (detaillierte Darstellung siehe Anhang) • There did not appear to be any impact of the degree of liver fibrosis on SVR rates in the two peginterferon alfa-2a studies that reported it. It should be noted that numbers of children in some of these subgroups were very small and none of the studies was powered for subgroup analysis, therefore results should be interpreted with caution. • Rates of non-response were variable, ranging from 12% to 25% (two peginterferon alfa-2a studies) and 17% to 51% (three peginterferon alfa-2b studies). A relapse rate of 17% was reported by one peginterferon alfa-2a study and a range of 3–17% across four peginterferon alfa-2b studies. (detaillierte Darstellung siehe Anhang) <u>Quality of life</u> • In one peginterferon alfa-2a study, a clinically significant decline was reported in physical health (15% of children) and in the QoL depression score (5% of children) 24 weeks after starting treatment, but most children showed no clinical changes in any of the measures of QoL, behaviour, depression or executive function at 24 weeks. For children who completed 48 weeks of treatment, there were no statistical differences from baseline for any of the QoL outcome measures after 1 or 2 years of follow-up (detaillierte Darstellung siehe Anhang) <u>Height or weight</u> • For one peginterferon alfa-2a study, there were no statistically significant changes in height nor weight from baseline to follow-up. For peginterferon alfa-2b, there was either no impact on height and weight, or rates decreased during treatment but recovered at the end of treatment or follow-up. • The impact on growth was often presented only in a brief narrative so results are not reliable. <u>Adverse events</u> • Although not consistently reported, the most frequently occurring adverse events were largely similar across all the studies and were typical of those associated with peginterferon and RBV. These included flu-like symptoms, headache, myalgia and/or arthralgia, gastrointestinal symptoms, injection site reactions, anaemia, leukopenia and neutropenia. (detaillierte Darstellung siehe Anhang) • Serious adverse events occurred at relatively low incidence rates of 4–6% in the two peginterferon alfa-2a studies that reported them.

	• The 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). Dose modifications occurred at a rate of 23–51% in two peginterferon alfa-2a studies, while one small peginterferon alfa-2b study reported no modifications and one other was unclear because of inconsistent reporting. Adverse events leading to dose modification were usually anaemia and neutropenia. Evidenzbasis: 46. Al Ali J, Owayed S, Al-Qabandi W, Husain K, Hasan F. Pegylated interferon alfa-2b plus ribavirin for the treatment of chronic hepatitis C genotype 4 in adolescents. Ann Hepatol 2010;9:156–60. 47. Ghaffar TY, El Naghy S, El Sebaie H, El Monaiery M, Ghaffar AY. Pegylated alpha interferon 2B plus ribavirin in the treatment of HCV genotype 4 infection. Indian J Pediatr 2009;76:895–8. http://dx.doi.org/10.1007/s12098-009-0187-x 48. 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. http://dx.doi.org/10.1097/INF.0b013e318159836c 51. Pawlowska M, Pilarczyk M, Halota W. Virologic response to treatment with Pegylated Interferon alfa-2b and Ribavirin for chronic hepatitis C in children. Med Sci Monit 2010;16:CR616–21. 56. Schwarz KB, Gonzalez-Peralta RP, Murray KF, Molleston JP, Haber BA, Jonas MM, et al. The combination of ribavirin and peginterferon is superior to peginterferon and placebo for children and adolescents with chronic hepatitis C. Gastroenterology 2011;140:450–8. http://dx.doi.org/ 10.1053/j.gastro.2010.10.047 57. 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. http://dx.doi.org/10.1016/j.jhep.2010.01.028 59. 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. http://dx.doi.org/10.1016/j.jhep.2010.01.016
	4. Fazit der Autoren: Treatment of children and young people with peginterferon (alfa-2a or -2b) and RBV may be an effective therapy. […] However, the available evidence is of poor quality. Future research into the impact of these treatments on growth and quality of life in children and young people is recommended. 5. Hinweise zum Review • Funding teilweise durch pharmazeutische Unternehmen, Interessenskonflikte der Autoren möglich

Leitlinien

WHO, 2016 [5]. **World Health Organization** GUIDELINES FOR THE SCREENING, CARE AND TREATMENT OF PERSONS WITH CHRONIC HEPATITIS C INFECTION UPDATED VERSION APRIL 2016	Fragestellung/Zielsetzung: The objective of these guidelines is to provide evidence-based recommendations on screening for, and the care and treatment of, persons with chronic hepatitis C virus (HCV) infection. They are primarily intended to provide a framework for the development or strengthening of hepatitis C treatment programmes.
	Methodik • WHO Steering Committee oversaw guidelines development process • Guidelines Development Group was constituted to ensure representation from various stakeholder groups, including members of organizations that represent persons living with HCV infection, advocacy groups, researchers and clinicians • Steering Committee proposed potential topics for developing recommendations and formulated these in the PICO format (PICO: Population, Intervention, Comparison, Outcomes) • Disussion at several web-enabled conference calls • Systematic reviews and meta-analyses were undertaken to assess the comparative safety and efficacy of treatment regimens • quality of the evidence was assessed using predefined criteria • meeting of the Guidelines Development Group, for each of the PICO questions • the results of the systematic reviews and network meta analyses were presented, and the evidence profiles and decision-making tables were reviewed • Recommendations were then formulated based on the overall quality of the evidence, in addition to the balance between benefits and harms, values and preferences, and resource implications • wording finalized by the entire group. • to document consensus, the Chair asked Group members whether they agreed with the recommendation • All Group members agreed with all the recommendations. • Internal and external review • Declaration of intrest reported by all members • Additionally: a network meta-analysis was conducted LoE: using GRADE approach **TABLE 4.1** GRADE categories of quality of evidence *(118)* • 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: strong (the panel was confident that the benefits of the

	intervention outweighed the risks) or conditional (the panel considered that the benefits of the intervention probably outweighed the risks).
	7.1 Assessment for HCV treatment Recommendation: All adults and children with chronic HCV infection, including people who inject drugs, should be assessed for antiviral treatment → *Strong recommendation, moderate quality of evidence* Hintergrund: One systematic review, including four RCTs and 31 non-randomized studies on the virological outcomes and adverse effects of treatment among children, showed that treatment success rates with interferon-based regimens are similar in children and adults (174). The overall SVR rate for pegylated interferon and ribavirin was 30–100%, which is comparable to SVR rates seen in adults. Adverse effects were primarily flu-like symptoms and neutropenia. Data were insufficient to assess the applicability of stopping therapy at week 12 if there was less than a 2 log reduction in HCV RNA, or the efficacy of shortening treatment duration to 24 weeks in children with genotypes 2 and 3 infection. **7.2 Treatment with direct-acting antiviral agents** Empfehlung stellt allein auf Erwachsene ab. **7.5 Treatment with pegylated interferon and ribavirin** Recommendation: Pegylated interferon in combination with ribavirin is recommended for the treatment of chronic HCV infection rather than standard non-pegylated interferon with ribavirin → *Strong recommendation, moderate quality of evidence* Hintergrund: „Although the treatment for HCV infection is moving away from the use of interferon, it is still the only recommended medicine for children and Adolescents […]. When treatment regimens include interferon, the pegylated formulation is the accepted standard of care in high-income countries because it has a longer half-life, resulting in the need for less frequent injections and because it results in higher SVR rates than standard interferon.“ *Quellen: Web Appendix 3, S. 8: Indirect evidence: The first [review] assessed clinical trials to investigate the safety and efficacy of pegylated interferon plus ribavirin for the treatment of chronic HCV in children and adolescents [7]. Eight trials were included in the review, with results indicating that over half (58%; 95% CI: 53-64) of patients aged 3-18 years who were administered pegylated interferon alpha-2a or 2b achieved SVR. SVR was higher for those with HCV genotypes 2 or 3 compared to 1 or 4. Four percent of patients discontinued treatment due to adverse events. Overall, the review findings indicated that pegylated interferon plus ribavirin is effective and safe in treating children and adolescents with HCV.*

Table 3: Indirect evidence from systematic reviews of HCV treatment in Children and PWID

Study, methods	No of studies (numbers and population)	Intervention Outcomes	Summary of primary findings (95% confidence interval)	Review conclusions
Druyts *et al.* (2013) Systematic review Cochrane/PRISMA compliant	1 RCT, 7 non-randomised trials (n=438, 3-18 year children/adolescents)	PEG+RBV for all patients Measured SVR, treatment discontinuation due to AE	Among children: • SVR: 58% (95%CI 53-64) • Treatment discontinuation due to AE: 4% (1-7%)	Treatment is effective and safe in treating children and adolescents with HCV

9.3 Considerations for Children and adolescents

None of the DAAs have been approved for use among children; thus, the only approved treatment for children remains pegylated interferon/ribavirin, which is recommended for children older than 2 years. Clinical trials are urgently needed to provide the necessary safety and efficacy data to allow regulatory approval of DAAs among children. The product literature for pegylated interferon reports that paediatric subjects treated with ribavirin combination therapy had a delay in weight and height increases after 48 weeks of therapy compared with baseline. However, by the end of 2 years of follow up, most subjects had returned to baseline normative growth curve percentiles for weight and height (mean weight-for-age percentile was 64% at baseline and 60% at 2 years' post-treatment; mean height percentile was 54% at baseline and 56% at 2 years' post-treatment).

Hinweise FBMed: Keine Genotyp-spezifischen Empfehlungen für Kinder/Jugendliche Patienten.

SIGN, 2013 [4].

Scottish Intercollegiate Guidelines Network

Management of hepatitis C

Fragestellung/Zielsetzung:
The guideline provides evidence based recommendations covering all stages of the patient care pathway; screening, testing, diagnosis, referral, treatment, care and follow up of infants, children and adults with, or exposed to, HCV infection.

Methodik

Grundlage der Leitlinie

- repräsentative Gremien - CoI-Erklärungen auf Anfrage einsehbar - öffentliche Konsultation und Expertenreview
- This guideline was issued in 2013 and will be considered for review in three years.
- Suchzeitraum: Databases searched include Medline, Embase, Cinahl, PsycINFO and the Cochrane Library. The year range covered was 2006-2012.
- Empfehlungen sind mit Literaturstellen verknüpft

LoE

LoE	
1++	High quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias
1+	well conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias
1 -	Meta-analyses, systematic reviews, or RCTs with a high risk of bias
2++	High quality systematic reviews of case control or cohort studies, high quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the

	relationship is causal
2+	Well conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal
2 -	Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
3	Non-analytic studies, eg case reports, case series
4	Expert opinion

GoR

A	At least one meta-analysis, systematic review, or RCT rated as 1++,and directly applicable to the target population; or A body of evidence consisting principally of studies rated as 1+, directly applicable to the target population, and demonstrating overall consistency of results
B	A body of evidence including studies rated as 2++, directly applicable to the target population, and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 1++ or 1+
C	A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 2++
D	Evidence level 3 or 4; or Extrapolated evidence from studies rated as 2+
GOOD PRACTICE POINTS	Recommended best practice based on the clinical experience of the guideline development group

Empfehlungen

6 Children and hepatitis C

Children infected with all genotypes of hepatitis C with evidence of moderate or severe liver disease should be considered for treatment with pegylated IFN and ribavirin. **(GoR: A)**

Children infected with HCV genotypes 2 and 3 should be considered for treatment with pegylated IFN and ribavirin irrespective of disease stage. **(GoR: B)**

In children with mild disease and infection with other genotypes, benefits of treatment need to be balanced against risks of side effects. **(GoR: C)**

The outcome in children after treatment with pegylated IFN and ribavirin is equivalent to that in adults. Side effects of treatment are seen with similar frequency and weekly injections cause distress. The advantages of achieving SVR early in life, eliminating the risk of onward transmission (particularly before girls reach child bearing age) and before the onset of chronic liver disease, will outweigh these disadvantages in many children infected with favourable genotypes. However, for those with less favourable genotypes and no evidence of chronic liver disease, it is appropriate to wait until more effective and

	acceptable treatment becomes available. Treatment of children with genotype 1 disease using protease inhibitors should only be considered as part of a clinical trial. **(GoR: Good practice point**) Response rates to treatment in children are of a similar magnitude to, and show the same influences of genotype, as adults (see section 10).[60] Combination treatment with interferon (IFN) and ribavirin gives an overall SVR of 50-60%.[60-63] There is potential for effects on thyroid function and growth problems.[62, 63] **(LoE: 3)** *Quellen: 60-63:* *60. Wirth S, Pieper-Boustani H, Lang T, Ballauff A, Kullmer U, Gerner P, et al. Peginterferon alpha 2b plus ribavirin treatment in children and adolescents with chronic hepatitis C. Hepatology 2005;41(5):1013-8.* *61. Süoğlu DOD, Elkabes B, Sökücü S, Saner G. Does interferon and ribavirin combination treatment increase the rate of treatment response in children with hepatitis C? J Pediatr Gastroenterol Nutr 2002;34(2):199-206.* *62. Wirth S, Lang T, Gehring S, Gerner P. Recombinant alpha interferon plus ribavirin in children and adolescents with chronic hepatitis C. Hepatology 2002;36(5):1280-4.* *63. Christensson B, Wiebe T, Akesson A, Widell A. Interferon alpha and ribavirin treatment of hepatitis C in children with malignancy in remission. Clin Infect Dis 2000;30(3):585-6.* Combination therapy with pegylated IFN and ribavirin is superior to pegylated interferon alone, and results in outcomes similar to that in adult studies (see section 10).[10] **(LoE: 1+)** *Quelle: 10: Schwarz KB, Gonzalez-Peralta RP, Murray KF, Molleston JP, Haber BA, Jonas MM, et al. The combination of ribavirin and peginterferon is superior to peginterferon and placebo for children and adolescents with chronic hepatitis C. Gastroenterology 2011;140(2):450-8.e1.* Combination treatment with interferon and ribavirin gives an SVR rate of 80-93% in children with genotype 3 infection, but only 47-59% in those with genotype 1 disease, which is similar to those in adult studies.[10, 64, 65] **(LoE: 2+)** *Quellen: 10, 64, 65* *10 Schwarz KB, Gonzalez-Peralta RP, Murray KF, Molleston JP, Haber BA, Jonas MM, et al. The combination of ribavirin and peginterferon is superior to peginterferon and placebo for children and adolescents with chronic hepatitis C. Gastroenterology 2011;140(2):450-8.e1.* *64. 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. Journal of Hepatology 2010;52(4):501-7.* *65. 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. Journal of Hepatology 2010;52(6):827-31.* *<u>Hinweis FBMed</u>: Keine spezifischen Empfehlungen für Kinder/Jugendliche zu den Genotypen 4-6.*
Mack CL et al., 2012 [2]. **(North American**	Fragestellung: to review the available data in children and provide clinicians with approaches to the diagnosis, management, and prevention of HCV infection in children and adolescents. The guideline details the

Society for Pediatric Gastroenterology, Hepatology, and Nutrition) **NASPGHAN Practice Guidelines: Diagnosis and Management of Hepatitis C Infection in Infants, Children, and Adolescents**	epidemiology and natural history of HCV infection in children, the diagnostic workup, monitoring and treatment of disease, and provides an update on future treatment options and areas of research.
	Methodik: • Group of experts in pediatric hepatology appointed by NASPGHAN (North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition) • Pediatric patients (age bracket: 0–18 years) = target population • systematic literature search was performed using accessible databases of relevance: PubMed, MEDLINE, EMBASE, Cochrane Library, Biosis Previews, EBM Reviews, ISI Web of Science, and Scopus including publications from 1990 to January 2011 • Auswahl der Literatur und Konsentierung der Empfehlung unklar • Keine CoI GoR und LoE: TABLE 1. Grading systems for recommendations Grading of recommendations, assessment, development and evaluation (GRADE) — Criteria Strength of recommendation 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 Quality of evidence 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 IMPAACT pediatrics grading system — Quality of evidence for recommendation Strength of recommendation A: Strong recommendation for the statement — I: One or more randomized trials in children† with clinical outcomes and/or validated laboratory endpoints B: Moderate recommendation for the statement — I*: One or more randomized trials in adults with clinical outcomes and/or validated laboratory endpoints with accompanying data in children† from one or more well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes C: Optional recommendation for the statement — II: One or more well-designed, nonrandomized trials or observational cohort studies in children† with long-term clinical outcomes II*: One or more well-designed, nonrandomized trials or observational cohort studies in adults with long-term clinical outcomes with accompanying data in children† from one or more smaller nonrandomized trials or cohort studies with clinical outcome data III: Expert opinion IMPAACT = International Maternal Pediatric Adolescent AIDS Clinical Trial. †Studies that include children or adolescents but not studies limited to postpubertal adolescents. *Anmerkung FB-Med: LL entspricht erfüllt nicht alle Qualitätsanforderungen (fehlende Infos zur Auswahl der Literatur, zur Konsentierung der Empfehlungen, Empfehlungen nicht immer mit LoE und GoR versehen). Darstellung dieser Quelle erfolgte aufgrund des kleinen Evidenzkörpers.*
	Empfehlungen **Treatment** Children with hepatitis C who demonstrate persistently elevated serum aminotransferases or those with progressive disease (ie fibrosis on liver histology) should be considered for treatment. Presently available treatments for pediatric CHC are IFN-a or PEG-IFN-a and ribavirin. The AASLD recommends the FDA-approved combination of PEG-IFN-a with ribavirin as first-line treatment for CHC in adults and children ages 3 to 17 years (81) **(1A; AI).**

	Combination treatment with PEG-IFN-a has demonstrated superiority in achieving sustained virological response (SVR) over IFN-a alone. The addition of ribavirin to IFN-a treatment dramatically improved SVR (up to 30%–40%) and the end-of-treatment response (ETR) in adults and children (102). Combination treatment also results in a significant decrease in the relapse rate of HCV infection as compared with PEG-IFN-a monotherapy (114,115). These advantages have also been confirmed in pediatric trials (102,106). The recommended length of therapy is 48 weeks of treatment for genotypes 1 or 4 and 24-week duration of treatment for genotypes 2 or 3 in children (1A; A1). If HCV RNA does not become undetectable by 24 weeks, there is also no evidence that prolonged treatment improves clinical outcome (ie, cirrhosis, HCC, SVR) (123). *Evidenzbasis:* 81. Ghany MG, Strader DB, Thomas DL, et al. Diagnosis, management, and treatment of hepatitis C: an update. Hepatology 2009;49:1335–74. 102. Schwarz KB, Gonzalez-Peralta RP, Murray KF, et al. The combination of ribavirin and peginterferon is superior to peginterferon and placebo for children and adolescents with chronic hepatitis C. Gastroenterology 2011;140:450–8. 106. Christensson B, Wiebe T, Akesson A, et al. Interferon-alpha and ribavirin treatment of hepatitis C in children with malignancy in remission. Clin Infect Dis 2000;30:585–6. 114. McHutchison JG, Gordon SC, Schiff ER, et al. Interferon alfa-2b alone or in combination with ribavirin as initial treatment for chronic hepatitis C. Hepatitis Interventional Therapy Group. N Engl J Med 1998;339:1485–92. 115. Poynard T, Marcellin P, Lee SS, et al. Randomized trial of interferon alpha2b plus ribavirin for 48 weeks or for 24 weeks versus interferon alpha2b plus placebo for 48 weeks for treatment of chronic infection with hepatitis C virus. International Hepatitis Interventional Therapy Group (IHIT). Lancet 1998;352:1426–32. 123. Di Bisceglie AM, Shiffman ML, Everson GT, et al., HALT-C Trial Investigators Prolonged therapy of advanced chronic hepatitis C with low-dose peginterferon. N Engl J Med 2008;359:2429–41. **FUTURE THERAPIES AND AREAS OF RESEARCH FOCUS** Recently 2 NS3/ 4a protease inhibitors were approved by the FDA for use in adults with CHC. These medications are combined with PEG-IFN-a and ribavirin and specifically target genotype 1 virus. In treatment naı¨ve individuals, sustained viral response rates of up to 80% have been demonstrated (174,175). These medications are the first direct-acting antivirals against HCV and show tremendous promise in the treatment of the most recalcitrant virus. They merit investigation in children and adolescents; however, protease inhibitors have not been studied in children and there are no published pharmacokinetic data or pediatric safety data. Thus, protease inhibitors should only be used in children in the context of a clinical trial **(2B; CIII).** **Side effects:** The pediatric population is uniquely susceptible to deficits in growth in both weight and height while receiving PEG-IFN-a and ribavirin. Both PEG-IFN-a and ribavirin can be associated with anorexia, nausea, and subsequent weight loss.

	With regard to growth in height, inhibition of growth velocity was observed in 70% of patients. Growth velocity increased after treatment completion, and at 24-week follow-up, the mean height percentile of 44.3% was slightly below the baseline height percentile of 50.9%. Long-term follow-up of growth parameters is necessary to determine whether the growth inhibition is temporary or long-lasting. *Hinweis FBMed: Keine weiteren Genotyp-spezifischen Empfehlungen angegeben.*

Ergänzende Dokumente anderer Organisationen zu möglichen Komparatoren

NICE, 2013 [3]. **Technology appraisal guidance [TA300]** Peginterferon alfa and ribavirin for treating chronic hepatitis C in children and young people	**Empfehlung** Peginterferon alfa-2a plus ribavirin and peginterferon alfa-2b plus ribavirin are recommended as treatment options, within their licensed indications, for children and young people with chronic hepatitis C. Evidence base: • Schwarz et al 2011: RCT for treatment in people aged 5–18 years with chronic hepatitis C: using only data from the intervention arm (n=55) • Sokal et al. 2010, n=65: uncontrolled observational study Proposed benefits of the technology • Treatment with peginterferon alfa could provide a sustained virological response that could potentially last for the lifetime of the child or young person, effectively providing a cure. • Treatment with peginterferon alfa in young children could help avoid the social stigma associated with hepatitis C infection. Treatment duration: • Peginterferon alfa-2a: The recommended treatment duration is 24 weeks (genotypes 2 or 3) or 48 weeks (all other genotypes) depending on baseline viral load and whether or not a child has a virological response (defined as a 100-fold decrease in, or undetectable levels of, serum HCV RNA) at week 24. Virological response by week 24 is predictive of sustained virological response. If adverse reactions occur, the dose can be reduced. • Peginterferon alfa-2b: The recommended treatment duration is 48 weeks for children and adolescents with genotype 1 or 4. Treatment should be stopped after 12 weeks if serum HCV RNA decreases less than 100-fold compared with pre-treatment levels or if serum HCV RNA is detectable at week 24. For children and adolescents with genotype 2 or 3, treatment is 24 weeks. If adverse reactions occur, the dose can be reduced. Adverse events • The main adverse reactions are: severe psychiatric and central nervous system effects, particularly depression, suicidal ideation and attempted suicide, weight loss and growth inhibition. The Committee concluded that peginterferon alfa has an impact on children's growth, but the problem of progressive liver disease outweighs the problems associated with being shorter than a child would otherwise have been without treatment. Evidence for clinical effectiveness • The systematic reviews conducted by the manufacturers and the Assessment Group identified few relevant studies in children and young people and these studies were small and of generally poor quality. The evidence base largely comprised single-arm studies • The Assessment Group showed that, among other uncertainties, conducting an accurate assessment of the generalisability of the studies was difficult because of substantial variation in the patient inclusion criteria and the countries represented. • Studies were presented to support the contention that children are

	'cured' following peginterferon alfa plus ribavirin treatment. The studies that followed children with sustained virological responses 5 years on showed that the children remained healthy, but these studies were small and not necessarily representative of the UK population. The Committee would have expected data from trials in adults to be presented in order to augment the evidence of the likelihood of an enduring response from peginterferon alfa plus ribavirin in children. • The Committee was aware that the population identified in the scope specified children and young people who have not previously been treated for HCV. It heard that clinicians do not offer re-treatment to children and young people previously treated with peginterferon plus ribavirin. Instead, when treatment has not resulted in a sustained virological response, these children and young people might be enrolled in a clinical trial of a newer technology or offered further treatment options (such as boceprevir or telaprevir) from 18 years of age, in line with guidelines for the treatment of adults with chronic hepatitis C. • Experience suggests that early treatment with peginterferon alfa plus ribavirin is better than later treatment, but the decision about whether and when to treat should be made by parents or carers together with the child or young person's clinician. • Both peginterferon alfa-2a studies (Schwarz et al., Sokal et al.) and 1 peginterferon alfa-2b study (Wirth et al.) reported sustained virological responses according to baseline viral load. The results suggest that children and young people with a low baseline viral load (less than 500,000 IU/ml, or 600,000 IU/ml or less) appear to have higher proportions of sustained virological responses (range 70–79%) than those with a higher viral load (more than 500,000 IU/ml, or 600,000 IU/ml or more, range 49–55%). Sokal et al. and Wirth et al. reported that a higher proportion of children and young people with genotype 2 or 3 had a sustained virological response compared with those with genotype 1, 4, 5 or 6, regardless of viral load. Wirth et al. reported that, in people with genotype 1, the proportion having a sustained virological response was higher in those with low baseline viral load than in those with high baseline viral load (72% compared with 29%, p=0.0006). • The proportions of sustained virological responses in 2 of the studies presented were higher in children and young people who had not been previously treated (55–62%) compared with those who had been previously treated (17–33%). The Pawlowska et al. study presented sustained virological response by genotype subgroup, but the numerators in each subgroup did not add up correctly to the total number of treatment-naive and previously treated patients in the trial (because study participants with genotype 3 HCV were excluded), and the numbers in these subgroups were small.

Detaillierte Darstellung der Recherchestrategie

Cochrane Library (Cochrane Database of Systematic Reviews, Health Technology Assessment Database) am 28.11.2016

#	Suchfrage
1	MeSH descriptor: [Hepatitis C, Chronic] explode all trees
2	(HCV):ti,ab,kw
3	chronic:ti,ab,kw and (hepatitis:ti,ab,kw next c:ti,ab,kw)
4	#1 or #2 or #3
5	#4 from 2011 to 2016

SR, HTAs in Medline (PubMed) am 29.11.2016

#	Suchfrage
1	hepatitis C, chronic/drug therapy[Mesh] OR hepatitis C, chronic/therapy[Mesh]
2	((chronic[Title/Abstract]) AND hepatitis[Title/Abstract]) AND c[Title/Abstract]
3	„HCV“[Title/Abstract]
4	(#2) OR #3
5	(#4) AND ((((((drug[Title/Abstract]) OR (drug therap*)[Title/Abstract]) OR therapy[Title/Abstract]) OR therapies[Title/Abstract]) OR treat[Title/Abstract]) OR treatment*[Title/Abstract])
6	(#1) OR #5
7	"hepatitis C, chronic"[Mesh] AND "drug therapy"[MeSH]
8	(#6) OR #7
9	(#8) AND ((Meta-Analysis[ptyp] OR systematic[sb] OR Technical Report[ptyp]) OR (((((trials[Title/Abstract] OR studies[Title/Abstract] OR database*[Title/Abstract] OR literature[Title/Abstract] OR publication*[Title/Abstract] OR Medline[Title/Abstract] OR Embase[Title/Abstract] OR Cochrane[Title/Abstract] OR Pubmed[Title/Abstract])) AND systematic*[Title/Abstract] AND (search*[Title/Abstract] OR research*[Title/Abstract]))) OR ((((((((((HTA[Title/Abstract]) OR technology assessment*[Title/Abstract]) OR technology report*[Title/Abstract]) OR (systematic*[Title/Abstract] AND review*[Title/Abstract])) OR (systematic*[Title/Abstract] AND overview*[Title/Abstract])) OR meta-analy*[Title/Abstract]) OR (meta[Title/Abstract] AND analyz*[Title/Abstract])) OR (meta[Title/Abstract] AND analys*[Title/Abstract])) OR (meta[Title/Abstract] AND analyt*[Title/Abstract]))) OR (((review*[Title/Abstract]) OR overview*[Title/Abstract]) AND ((evidence[Title/Abstract]) AND based[Title/Abstract]))))
10	(((#9) AND ("2011/11/01"[PDAT] : "2016/11/29"[PDAT])) NOT "The Cochrane database of systematic reviews"[Journal]) NOT (animals[MeSH:noexp] NOT (Humans[MesH] AND animals[MeSH:noexp]))

Leitlinien in Medline (PubMed) am 29.11.2016

#	Suchfrage
1	"hepatitis C, chronic"[Mesh] OR (((chronic[Title/Abstract]) AND hepatitis[Title/Abstract]) AND c[Title/Abstract])

2	(#1) AND (Guideline[ptyp] OR Practice Guideline[ptyp] or guideline*[Title] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp] OR recommendation*[Title/Abstract])
3	(((#2) AND ("2011/11/01"[PDAT] : "2016/11/29"[PDAT])) NOT ((comment[Publication Type]) OR letter[Publication Type])) NOT (animals[MeSH:noexp] NOT (Humans[MesH] AND animals[MeSH:noexp]))

Literatur:

1. **Hartwell D, Cooper K, Frampton GK, Baxter L, Loveman E.** 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 (Structured abstract) [online]. In: Health Technology Assessment Database. Health Technology Assessment; 2014. [Zugriff: 4]. URL: http://onlinelibrary.wiley.com/o/cochrane/clhta/articles/HTA-32013001084/frame.html.

2. **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(6):838-855.

3. **National Institute for Health and Care Excellence (NICE).** Peginterferon alfa and ribavirin for treating chronic hepatitis C in children and young people [online]. London (GBR): NICE; 2006. [Zugriff: 29.11.2016]. (NICE technology appraisal guidance; Band 300). URL: https://www.nice.org.uk/guidance/ta300/resources/peginterferon-alfa-and-ribavirin-for-treating-chronic-hepatitisc-in-children-and-young-people-82602359258821.

4. **Scottish Intercollegiate Guidelines Network (SIGN).** Management of hepatitis C. A national clinical guideline. [online]. Edinburgh (GBR): Scottish Intercollegiate Guidelines Network (SIGN); 07.2013. [Zugriff: 29.11.2016]. (SIGN publication; Band 133). URL: http://www.sign.ac.uk/pdf/sign133.pdf.

5. **World Health Organization (WHO).** Guidelines for the Screening Care and Treatment of Persons with Chronic Hepatitis C Infection: Updated Version. Geneva; World Health Organization 2016.; 2016. Apr.

Anhang:

Hartwell, D. et al., 2014 [1]: 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

TABLE 5 Sustained virological response according to genotype

		SVR according to genotype	
Study	Treatment	Genotype	SVR, % (*n*/*N*)
Schwarz *et al.*, 2011[56]	PEG α-2a + RBV	Genotype 1	47, 95% CI 32 to 61 (21/45)
	48 weeks, $n = 55$	Genotypes 2–6[a]	80, 95% CI 55 to 100 (8/10)
Sokal *et al.*, 2010[57]	PEG α-2a + RBV	Genotype 1, 4, 5 or 6[b]	57 (27/47) (one ND)
	24 or 48 weeks, $n = 65$	Genotype 2 or 3	89 (16/18) (one ND)
Pawlowska *et al.*, 2010[51]	PEG α-2b + RBV	Genotype 1	48 (13/27)
	24 or 48 weeks, $n = 53$	Genotype 3	50 (1/2)
		Genotype 4	50 (12/24)
Wirth *et al.*, 2010[59]	PEG α-2b + RBV	Genotype 1	53 (38/72)
	24 or 48 weeks, $n = 107$	Genotype 2 or 3	93 (28/30)
		Genotype 4	80 (4/5)
Jara *et al.*, 2008[48]	PEG α-2b + RBV	Genotype 1	46 (12/26)
	24 or 48 weeks, $n = 30$	Genotype 3	100 (3/3)
		Genotype 4	0 (0/1)

CI, confidence interval; ND, not defined by authors but assumed to be 'not determined'; PEG α-2a, peginterferon alfa-2a; PEG α-2b, peginterferon alfa-2b.
a No participants with genotypes 4, 5 or 6, thus all are genotype 2 or 3.
b $n = 2$ participants with genotypes 4, 5 or 6 and $n = 45$ with genotype 1.

TABLE 7 Sustained virological response according to previous treatment history

Study	Treatment	SVR according to previous treatment	
		Treatment history	SVR, % (*n*/*N*)
Pawlowska *et al.*, 2010[51]	PEG α-2b + RBV	Treatment naive	62 (18/29)[a]
	24 or 48 weeks, *n* = 53	Genotype 1	62 (10/16)
		Genotype 3	50 (1/2)
		Genotype 4	72 (8/11)
		Previously treated	33 (8/24)[a]
		Genotype 1	27 (3/11)
		Genotype 3	N/A[b]
		Genotype 4	30 (4/13)
Jara *et al.*, 2008[48]	PEG α-2b + RBV	Treatment naive	55 (11/20)[c]
	24 or 48 weeks, *n* = 30	Previously treated	17 (1/6)[c]

N/A, not applicable; PEG α-2b, peginterferon alfa-2b.
a Numerators in the genotype subgroups (as reported in the publication) do not add up correctly to the total number of treatment-naive and previously treated participants.
b No previously treated patients had genotype 3.
c Of 30 patients, only 26 were included, all genotype 1; the remaining four patients (3 × genotype 3, 1 × genotype 4, all treatment naive) were not included.

TABLE 11 Non-response and relapse

Study	Treatment	Non-response, % (*n*/*N*)	Relapse, % (*n*/*N*)
Schwarz *et al.*, 2011[56] + related publication[28]	PEG α-2a + RBV	25 (14/55)	17 (9/55)[a]
	48 weeks, *n* = 55		
Sokal *et al.*, 2010[57]	PEG α-2a + RBV	12 (8/65)[b]	NR
	24 or 48 weeks, *n* = 65		
Al Ali *et al.*, 2010[46]	PEG α-2b + RBV	17 (2/12)	8 (1/12)
	48 weeks, *n* = 12		
Pawlowska *et al.*, 2010[51] + abstract[52]	PEG α-2b + RBV	51 (27/53)	17 (9/53)[c]
	24 or 48 weeks, *n* = 53		
Wirth *et al.*, 2010[59]	PEG α-2b + RBV	NR	12 (9/72)[d]
	24 or 48 weeks, *n* = 107		8 (9/107)[e]
Jara *et al.*, 2008[48]	PEG α-2b + RBV	47 (14/30)	3 (1/30)
	24 or 48 weeks, *n* = 30		

NR, not reported; PEG α-2a, peginterferon alfa-2a; PEG α-2b, peginterferon alfa-2b.
a *n* calculated by reviewer.
b All patients with non-response had genotypes 1, 4, 5 or 6 (none had genotype 2 or 3).
c Abstract reports a relapse rate of 7.5% for whole group but assumed to be an error.
d *n* calculated by reviewer; all patients who relapsed had genotype 1.
e Calculated by reviewer for whole cohort.

TABLE 13 Changes in QoL at 24 weeks

QoL outcome	Mean ± SD baseline score	Mean ± SD score at 24-week follow-up	Clinically significant improvement, % (*n*/*N*)	Clinically significant decline, % (*n*/*N*)	No clinical change, % (*n*/*N*)	*p*-value for changes in mean scores
CHQ physical summary	52.1 ± 4.8	49.8 ± 7.5	0	15 (8/55)	86 (47/55)	0.013 (mean change 2.40 ± 6.8)
CHQ psychosocial summary	52.1 ± 7.9	52.3 ± 10.2	5 (3/55)	7 (4/55)	88 (48/55)	NR
CBCL internalising	52.4 ± 8.5	51.0 ± 11.0	4 (2/55)	5 (3/55)	91 (50/55)	NS
CBCL externalising	50.4 ± 9.4	48.8 ± 10.3	2 (1/55)	5 (3/55)	93 (51/55)	NS
CBCL total behaviour problem	51.5 ± 9.3	49.7 ± 10.2	2 (1/55)	4 (2/55)	95 (52/55)	NS
CDI total score	5.9 ± 4.2	6.2 ± 5.6	0	5 (3/55)	95 (52/55)	NS
BRIEF global executive composite	53.5 ± 9.9	52.2 ± 10.1	5 (3/55)	5 (3/55)	90 (49/55)	NS

NR, not reported; NS, not statistically significant ($p > 0.05$).
Scores are for all participants who received peginterferon alfa-2a in the PEDS-C trial ($n = 55$).[28,53,56]

TABLE 14 Adverse events

Event	PEG α-2a + RBV: incidence of event, % (*n*/*N*)		PEG α-2b + RBV: incidence of event, % (*n*/*N*)				
	Schwarz *et al.*, 2011[56] ($n = 55$)	Sokal *et al.*, 2010[57] ($n = 65$)	Al Ali *et al.*, 2010[46] ($n = 12$)	Pawlowska *et al.*, 2010[51] ($n = 53$)	Wirth *et al.*, 2010[59] ($n = 107$)	Ghaffar *et al.*, 2009[47] ($n = 7$)	Jara *et al.*, 2008[48] ($n = 30$)
Dose discontinuation							
AE	7 (4/55)[a]	3 (2/65)[b]	NR	NR	1 (1/107)	NR	10 (3/30)
Other reason[c]	NR	NR	NR	NR	0 (0/107)	NR	NR
Dose modification							
Any AE	51 (28/55)[d]	23 (15/65)	NR	NR	25 (27/107)	0 (0/7)	NR
Anaemia	11 (6/55)[d]	5 (3/65)	33 (4/12)	6 (3/53)	7 (7/107)[e]	NR	0 (0/30)
Neutropenia	NR	17 (11/65)	NR	NR	12 (13/107)	NR	23 (7/30)
Weight/ growth	NR	NR	NR	NR	10 (11/107)	NR	NR
Other reason	2 (1/55)[d]	6 (4/65)	NR	NR	24 (26/107)	NR	NR
Serious AE	4 (2/55)	6 (4/65)	NR	NR	0 (0/107)[f]	NR	NR
Death	NR	NR	NR	NR	0 (0/107)	NR	NR

AE, adverse event; NR, not reported; PEG α-2a, peginterferon alfa-2a; PEG α-2b, peginterferon alfa-2b.
a Two were considered serious adverse events; also reported in an abstract[55] that early discontinuation was 4%.
b Both were considered serious adverse events.
c Excluding discontinuation because of non-response to therapy.
d Reported in an abstract (Schwarz and colleagues[56]).
e The number of patients with dose modification due to anaemia was stated as seven and eight in different places in the original publication.[59]
f Assumed to be zero (authors stated that there were no treatment-related serious adverse events).