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## Table A. Grading system for recommendation (Grading of Recommendations Assessment Development and Evaluation - GRADE - system)

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| --- | --- |
| **Strength of recommendations** | |
| 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 |

## Appendix 1. Search strategy

The search query used in MEDLINE was:

((("hepatitis c virus"[All Fields] AND "treatment"[All Fields]) AND "child"[All Fields]) OR "peginterferon"[All Fields]) OR "direct acting antiviral"[All Fields] AND (("2007/01/01"[PDAT] : "2017/06/01"[PDAT]) AND "humans"[MeSH Terms] AND English[lang] AND ("infant"[MeSH Terms] OR "child"[MeSH Terms] OR "adolescent"[MeSH Terms]))

The search query used in Embase was:

'hepatitis c virus'/exp or 'hepatitis c virus' and ('child'/exp or child) and ('treatment'/exp or treatment) or 'peginterferon'/exp or peginterferon or 'direct acting antiviral agent'/exp or 'direct acting antiviral agent' and ([article]/lim or [article in press]/lim or [conference abstract]/lim) and [english]/lim and ([child]/lim or [adolescent]/lim) and [humans]/lim and ([embase]/lim or [medline]/lim) and [2007-2017]/py

## Appendix 2. Results of the initial PubMed search (n 594)

|  |  |
| --- | --- |
| **No and reference** | **Excluded / included and main reason for exclusion** |
| 1: Majekodunmi AO, Thorne C, Malyuta R, Volokha A, Callard RE, Klein NJ, Lewis J; European Paediatric HIV/HCV Co-infection Study group in the European Pregnancy and Paediatric HIV Cohort Collaboration and the Ukraine Paediatric HIV Cohort Study in EuroCoord. Modelling CD4 T Cell Recovery in Hepatitis C and HIV Co-infected Children Receiving Antiretroviral Therapy. Pediatr Infect Dis J. 2017 May;36(5):e123-e129. doi: 10.1097/INF.0000000000001478. PubMed PMID: 28403051; PubMed Central PMCID: PMC5380220. | Excluded, not pertinent to query search |
| 2: Wyles D, Saag M, Viani RM, Lalezari J, Adeyemi O, Bhatti L, Khatri A, King JR, Hu YB, Trinh R, Shulman NS, Ruane P. TURQUOISE-I Part 1b: Ombitasvir/Paritaprevir/Ritonavir and Dasabuvir with Ribavirin for Hepatitis C Virus Infection in HIV-1 Coinfected Patients on Darunavir. J Infect Dis. 2017 Feb 15;215(4):599-605. doi: 10.1093/infdis/jiw597. PubMed PMID: 28329334. | Excluded, not pertinent to query search |
| 3: Coppola N, Alessio L, Gualdieri L, Pisaturo M, Sagnelli C, Minichini C, Di Caprio G, Starace M, Onorato L, Signoriello G, Macera M, Angelillo IF, Pasquale G, Sagnelli E. Hepatitis B virus infection in undocumented immigrants and refugees in Southern Italy: demographic, virological, and clinical features. Infect Dis Poverty. 2017 Feb 9;6(1):33. doi: 10.1186/s40249-016-0228-4. PubMed PMID: 28179020; PubMed Central PMCID: PMC5299765. | Excluded, not pertinent to query search |
| 4: Karbalaie Niya MH, Salman-Tabar S, Bokharaei-Salim F, Behmanesh M, Keyvani H. Prevalence of resistant associated variants (RAVs) in the naïve HCV patient candidate for direct acting antiviral (DAA) therapy. Microb Pathog. 2017 Apr;105:166-170. doi: 10.1016/j.micpath.2017.01.060. Epub 2017 Feb 1. PubMed PMID: 28161357. | Excluded, not pertinent to query search |
| 5: Silvestri C, Bartolacci S, Pepe P, Monnini M, Voller F, Cipriani F, Stasi C. Attempt to calculate the prevalence and features of chronic hepatitis C infection in Tuscany using administrative data. World J Gastroenterol. 2016 Nov 28;22(44):9829-9835. PubMed PMID: 27956807; PubMed Central PMCID: PMC5124988. | Excluded, not pertinent to query search |
| 6: Hlaing NK, Banerjee D, Mitrani R, Arker SH, Win KS, Tun NL, Thant Z, Win KM, Reddy KR. Hepatitis C virus therapy with peg-interferon and ribavirin in Myanmar: A resource-constrained country. World J Gastroenterol. 2016 Nov 21;22(43):9613-9622. PubMed PMID: 27920482; PubMed Central PMCID: PMC5116605. | Excluded, not pertinent to query search |
| 7: Domagalski K, Pawłowska M, Zaleśna A, Pilarczyk M, Rajewski P, Halota W, Tretyn A. Impact of IL28B and OAS gene family polymorphisms on interferon treatment response in Caucasian children chronically infected with hepatitis B virus. World J Gastroenterol. 2016 Nov 7;22(41):9186-9195. PubMed PMID: 27895405; PubMed Central PMCID: PMC5107599. | Excluded, not pertinent to query search |
| 8: Sultana C, Oprişan G, Teleman MD, Dinu S; HepGen 88/2012 Project Team, Oprea C, Voiculescu M, Ruta S. Impact of hepatitis C virus core mutations on the response to interferon-based treatment in chronic hepatitis C. World J Gastroenterol. 2016 Oct 7;22(37):8406-8413. PubMed PMID: 27729747; PubMed Central PMCID: PMC5055871. | Excluded, not pertinent to query search |
| 9: El-Karaksy HM, Sharaf SA, Mandour IA, Mogahed EA, Rady NH, El-Mougy FA. 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 Dec;77(12):1248-1253. doi: 10.1016/j.humimm.2016.09.005. Epub 2016 Sep 19. PubMed PMID: 27660094. | Excluded, not satisfying eligibility criteria (viral genotype distribution not provided) |
| 10: Indolfi G, Nebbia G, Cananzi M, Maccabruni A, Zaramella M, D'Antiga L, Grisotto L, Azzari C, Resti M; and the Italian Study Group for Treatment of Chronic Hepatitis C in Children. Kinetic of Virologic Response to Pegylated Interferon and Ribavirin in Children With Chronic Hepatitis C Predicts the Effect of Treatment. Pediatr Infect Dis J. 2016 Dec;35(12):1300-1303. PubMed PMID: 27636721. | Included |
| 11: Czerwiński J, Lewandowska D, Małkowski P, Danielewicz R. Liver Transplant Registry in Poland: Web-Netted Quality Tool in Liver Transplantation From Deceased and Living Donors. Transplant Proc. 2016 Jun;48(5):1347-9. doi: 10.1016/j.transproceed.2016.01.059. PubMed PMID: 27496402. | Excluded, not pertinent to query search |
| 12: Lawitz E, Reau N, Hinestrosa F, Rabinovitz M, Schiff E, Sheikh A, Younes Z, Herring R Jr, Reddy KR, Tran T, Bennett M, Nahass R, Yang JC, Lu S, Dvory-Sobol H, Stamm LM, Brainard DM, McHutchison JG, Pearlman B, Shiffman M, Hawkins T, Curry M, Jacobson I. Efficacy of Sofosbuvir, Velpatasvir, and GS-9857 in Patients With Genotype 1 Hepatitis C Virus Infection in an Open-Label, Phase 2 Trial. Gastroenterology. 2016 Nov;151(5):893-901.e1. doi: 10.1053/j.gastro.2016.07.039. Epub 2016 Jul 30. PubMed PMID: 27486034. | Excluded, not pertinent to query search |
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| 14: Janjua NZ, Yu A, Kuo M, Alvarez M, Cook D, Wong J, Tyndall MW, Krajden M. Twin epidemics of new and prevalent hepatitis C infections in Canada: BC Hepatitis Testers Cohort. BMC Infect Dis. 2016 Jul 19;16:334. doi: 10.1186/s12879-016-1683-z. PubMed PMID: 27436414; PubMed Central PMCID: PMC4952323. | Excluded, not pertinent to query search |
| 15: Meng P, Zhao S, Niu X, Fu N, Su S, Wang R, Zhang Y, Qiao L, Nan Y. Involvement of the Interleukin-23/Interleukin-17 Axis in Chronic Hepatitis C Virus Infection and Its Treatment Responses. Int J Mol Sci. 2016 Jul 15;17(7). pii: E1070. doi: 10.3390/ijms17071070. Erratum in: Int J Mol Sci. 2016 Oct 26;17 (11):. PubMed PMID: 27428948; PubMed Central PMCID: PMC4964446. | Excluded, not pertinent to query search |
| 16: Mohamed AA, Sayed O, Ali OE, Sayed GA, Moustfa Z, Elagawy WA. MONOCYTE CHEMOTACTIC PROTEIN AND RESPONSE TO PEGYLATED INTERFERON-ALPHA-2A TREATMENT IN PATIENTS WITH CHRONIC HEPATITIS C (CHC) GENOTYPE 4. J Egypt Soc Parasitol. 2016 Apr;46(1):117-24. PubMed PMID: 27363047. | Excluded, not pertinent to query search |
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| 25: Zimmermann T, Hueppe D, Mauss S, Buggisch P, Pfeiffer-Vornkahl H, Grimm D, Galle PR, Alshuth U. Effects of Smoking on Pegylated Interferon alpha 2a and First Generation Protease Inhibitor-based Antiviral Therapy in Naïve Patients Infected with Hepatitis C Virus Genotype 1. J Gastrointestin Liver Dis. 2016 Mar;25(1):15-24. doi: 10.15403/jgld.2014.1121.251.a2a. PubMed PMID: 27014750. | Excluded, not pertinent to query search |
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| 27: Xie Y, Garza G, Dong J. Hepatitis C Virus Genotype and Subtype Distribution in Patient Specimens Tested at the University of Texas Medical Branch, Galveston, Between January 2011 and November 2014. Lab Med. 2016 May;47(2):112-8. doi: 10.1093/labmed/lmw004. Epub 2016 Mar 19. PubMed PMID: 26995188. | Excluded, not pertinent to query search |
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| 32: Wei L, Han T, Yang D, Heo J, Shang J, Cheng J, Chen X, Xie Q, Kim JH, Kalmeijer R, Ouwerkerk-Mahadevan S, Hoeben E, Lenz O, Verbinnen T, Sinha R, Li M, Scott J, Peeters M, Witek J; TIGER team. Simeprevir plus peginterferon/ribavirin for HCV genotype 1-infected treatment-naïve patients in China and South Korea. J Gastroenterol Hepatol. 2016 May;31(5):912-20. doi: 10.1111/jgh.13288. PubMed PMID: 26777137. | Excluded, not pertinent to query search |
| 33: Granot E, Sokal EM. Hepatitis C Virus in Children: Deferring Treatment in Expectation of Direct-Acting Antiviral Agents. Isr Med Assoc J. 2015 Nov;17(11):707-11. Review. PubMed PMID: 26757569. | Excluded, not pertinent to query search |
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| 37: Ohmer S, Honegger J. New prospects for the treatment and prevention of hepatitis C in children. Curr Opin Pediatr. 2016 Feb;28(1):93-100. doi: 10.1097/MOP.0000000000000313. Review. PubMed PMID: 26709684; PubMed Central PMCID: PMC4763928. | Excluded, not pertinent to query search |
| 38: van Meer S, van Erpecum KJ, Sprengers D, Coenraad MJ, Klümpen HJ, Jansen PL, IJzermans JN, Verheij J, van Nieuwkerk CM, Siersema PD, de Man RA. Hepatocellular carcinoma in cirrhotic versus noncirrhotic livers: results from a large cohort in the Netherlands. Eur J Gastroenterol Hepatol. 2016 Mar;28(3):352-9. doi: 10.1097/MEG.0000000000000527. PubMed PMID: 26629867. | Excluded, not pertinent to query search |
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| 41: Nagaoki Y, Aikata H, Nakano N, Shinohara F, Nakamura Y, Hatooka M, Morio K, Kan H, Fujino H, Kobayashi T, Fukuhara T, Masaki K, Ono A, Nakahara T, Kawaoka T, Miki D, Tsuge M, Hiramatsu A, Imamura M, Takahashi S, Kawakami Y, Ochi H, Chayama K; Hiroshima Liver Study Group. Development of hepatocellular carcinoma in patients with hepatitis C virus infection who achieved sustained virological response following interferon therapy: A large-scale, long-term cohort study. J Gastroenterol Hepatol. 2016 May;31(5):1009-15. doi: 10.1111/jgh.13236. PubMed PMID: 26584407. | Excluded, not pertinent to query search |
| 42: Benaiges D, Garcia-Retortillo M, Mas A, Cañete N, Broquetas T, Puigvehi M, Chillarón JJ, Flores-Le Roux JA, Sagarra E, Cabrero B, Zaffalon D, Solà R, Pedro-Botet J, Carrión JA. Clinical Value of Thyrotropin Receptor Antibodies for the Differential Diagnosis of Interferon Induced Thyroiditis. Exp Clin Endocrinol Diabetes. 2016 Jan;124(1):39-44. doi: 10.1055/s-0035-1565071. Epub 2015 Nov 17. PubMed PMID: 26575116. | Excluded, not pertinent to query search |
| 43: Tiedemann LM, Manley P, Smith ER, Dagi LR. Visual Field Loss in a Case of Recurrent Cystic Craniopharyngioma During Concomitant Treatment With Pegylated Interferon α-2b. J Pediatr Hematol Oncol. 2016 Jan;38(1):e26-8. doi: 10.1097/MPH.0000000000000468. PubMed PMID: 26558808. | Excluded, not pertinent to query search |
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## Appendix 3. Results of the initial Embase search (n 767)

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| **No and reference** | **Excluded / included and main reason for exclusion** |
| 1. Association of polymorphisms in key Th-17 immune response genes with HBeAg-positive chronic hepatitis B susceptibility and response to PEG-IFNa-2α Ju H. Liu H. Tian Z.-B. Jiang Y.-P. Zhang C.-P. Liu X.-S. Virology (2017) 509 (35-41). Date of Publication: 1 Sep 2017 | Excluded, not pertinent to query search |
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| 4. Impact of IL28B gene polymorphism on virological response to pegylated interferon/Ribavirin therapy in Egyptian children with HCV genotype-4 chronic hepatitis Megahed A. Abdalla A. Zalata K. Fathy A. Barakat T. El-Latief M.A. El-Zainy S. El-Mabood S.A. Journal of Pediatric Gastroenterology and Nutrition (2017) 64 Supplement 1 (610). Date of Publication: 1 Apr 2017 | Excluded, not satisfying eligibility criteria (conference abstract on IFN-based treatment) |
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| 728. Serum IL-18 concentration does not depend on the presence of HCV-RNA in serum or in PBMC Majda-Stanisławska E. Pietrzak A. Brzezińska-Błaszczyk E. Hepato-Gastroenterology (2008) 55:81 (212-215). Date of Publication: January/February 2008 | Excluded, not pertinent to query search |
| 729. Kidney graft survival in patients with hepatitis C: A single center experience Arango J.L. Arbelaez M. Henao J. Mejia G. Arroyave I. Carvajal J. Garcia A. Gutierrez J. Velásquez A. Garcia L. Aguirre C. Clinical Transplantation (2008) 22:1 (16-19). Date of Publication: January/February 2008 | Excluded, not pertinent to query search |
| 730. Treatment of chronic hepatitis B in children Kansu A. Recent Patents on Anti-Infective Drug Discovery (2008) 3:1 (64-69). Date of Publication: January 2008 | Excluded, not pertinent to query search |
| 731. Hepatitis C virus infection and risk of posttransplantation lymphoproliferative disorder among solid organ transplant recipients Morton L.M. Landgren O. Chatterjee N. Castenson D. Parsons R. Hoover R.N. Engels E.A. Blood (2007) 110:13 (4599-4605). Date of Publication: 15 Dec 2007 | Excluded, not pertinent to query search |
| 732. Seroprevalence of hepatitis B and C viral co-infections among children infected with human immunodeficiency virus attending the paediatric HIV care and treatment center at Muhimbili National Hospital in Dar-es-Salaam, Tanzania Telatela S.P. Matee M.I. Munubhi E.K. BMC Public Health (2007) 7 Article Number: 338. Date of Publication: 2007 | Excluded, not pertinent to query search |
| 733. Design of the PEDS-C trial: Pegylated interferon +/- ribavirin for children with chronic hepatitis C viral infection Murray K.F. Rodrigue J.R. González-Peralta R.P. Shepherd J. Barton B.A. Robuck P.R. Schwarz K.B. Clinical Trials (2007) 4:6 (661-673). Date of Publication: 2007 | Excluded, not pertinent to query search |
| 734. Hepatitis C and B viruses among some high risk groups of Egyptian children Kandil M.E. Rasheed M.A. Saad N.E. Journal of Medical Sciences (2007) 7:8 (1259-1267). Date of Publication: 15 Nov 2007 | Excluded, not pertinent to query search |
| 735. Long-term response to highly active antiretroviral therapy in human immunodeficiency virus and hepatitis C virus coinfected children: 6 Years of follow-up Micheloud D. Jensen J. Bellón J.M. Gonzalez R. Mellado M.J. Navarro Ma.L. Muñoz-Fernández M.A. Resino S. Pediatric Infectious Disease Journal (2007) 26:11 (1061-1064). Date of Publication: November 2007 | Excluded, not pertinent to query search |
| 736. Adverse effects during the treatment with pegylated interferon and ribavirin in children with chronic hepatitis C Kowala-Piaskowska A. Mozer-Lisewska I. Figlerowicz M. Słuzewski W. Pharmacoepidemiology and Drug Safety (2007) 16:10 (1095-1103). Date of Publication: October 2007 | Excluded, duplicate publication |
| 737. Multivariable analysis comparing outcome after sentinel node biopsy or therapeutic lymph node dissection in patients with melanoma Van Akkooi A.C.J. Bouwhuis M.G. De Wilt J.H.W. Kliffen M. Schmitz P.I.M. Eggermont A.M.M. British Journal of Surgery (2007) 94:10 (1293-1299). Date of Publication: October 2007 | Excluded, not pertinent to query search |
| 738. Experience with 122 consecutive liver transplant procedures at King Faisal Specialist Hospital and Research Center Al-Sebayel M. Khalaf H. Al-Sofayan M. Al-Saghier M. Abdo A. Al-Bahili H. El-Sheikh Y. Helmy A. Medhat Y. Annals of Saudi Medicine (2007) 27:5 (333-338). Date of Publication: September/October 2007 | Excluded, not pertinent to query search |
| 739. A national sample of individuals who acquired hepatitis C virus infections in childhood or adolescence: Risk factors for advanced disease Harris H.E. Mieli-Vergani G. Kelly D. Davison S. Gibb D.M. Ramsay M.E. Journal of Pediatric Gastroenterology and Nutrition (2007) 45:3 (335-341). Date of Publication: September 2007 | Excluded, not pertinent to query search |
| 740. B-cell depletion in the treatment of mixed cryoglobulinemia Sansonno D. Tucci F.A. Montrone M. Troiani L. Sansonno L. Gatti P. Lauletta G. Digestive and Liver Disease (2007) 39:SUPPL. 1 (S116-S121). Date of Publication: September 2007 | Excluded, not pertinent to query search |
| 741. Clinical improvement of diffuse lymphangiomatosis with pegylated interferon alfa-2b therapy: Case report and review of the literature Ozeki M. Funato M. Kanda K. Ito M. Teramoto T. Kaneko H. Fukao T. Kondo N. Pediatric Hematology and Oncology (2007) 24:7 (513-524). Date of Publication: September 2007 | Excluded, not pertinent to query search |
| 742. Prevalence of hepatitis C and related factors among beta-thalassemia major patients in Southern Iran in 2005-2006 Ansari H. Kamani H. Arbabi Sarjo A. Journal of Medical Sciences (2007) 7:6 (997-1002). Date of Publication: 15 Aug 2007 | Excluded, not pertinent to query search |
| 743. Antiviral therapy for chronic hepatitis C in patients with inherited bleeding disorders: An international, multicenter cohort study Posthouwer D. Yee T.T. Makris M. Fischer K. Griffioen A. Van Veen J.J. Mauser-Bunschoten E.P. Journal of Thrombosis and Haemostasis (2007) 5:8 (1624-1629). Date of Publication: August 2007 | Excluded, not pertinent to query search |
| 744. Long-term follow-up of the hepatitis C HENCORE cohort: Response to therapy and occurrence of liver-related complications Pradat P. Tillmann H.L. Sauleda S. Braconier J.-H. Saracco G. Thursz M. Goldin R. Winkler R. Alberti A. Esteban J.-I. Hadziyannis S. Rizzetto M. Thomas H. Manns M.P. Trepo C. Journal of Viral Hepatitis (2007) 14:8 (556-563). Date of Publication: August 2007 | Excluded, not pertinent to query search |
| 745. Antagonistic expression of hepatitis C virus and alpha interferon in lymphoid cells during persistent occult infection Pham T.N.Q. Mulrooney-Cousins P.M. Mercer S.E. MacParland S.A. Inglot M. Zalewska M. Simon K. Michalak T.I. Journal of Viral Hepatitis (2007) 14:8 (537-548). Date of Publication: August 2007 | Excluded, not pertinent to query search |
| 746. Prevalence of hepatitis B, C, and delta virus infections among children in Mongolia: Progress in childhood immunization Tsatsralt-Od B. Takahashi M. Endo K. Agiimaa D. Buyankhuu O. Ninomiya M. Lorenzo F.R. Okamoto H. Journal of Medical Virology (2007) 79:8 (1064-1074). Date of Publication: August 2007 | Excluded, not pertinent to query search |
| 747. Rate of cirrhosis progression reduced in HIV/HCV co-infected non-responders to anti-HCV therapy De Bona A. Galli L. Gallotta G. Guzzo A. Alagna L. Lazzarin A. Uberti-Foppa C. New Microbiologica (2007) 30:3 (259-264). Date of Publication: July 2007 | Excluded, not pertinent to query search |
| 748. Do different hepatitis C virus genotypes behave differently? Amarapurkar D.N. Patel N.D. Rane P. Kamani P. Tropical gastroenterology : official journal of the Digestive Diseases Foundation (2007) 28:3 (99-104). Date of Publication: 2007 Jul-Sep | Excluded, not pertinent to query search |
| 749. Combined Liver and Kidney Transplantation: Analysis of Padova Experience Zanus G. Carraro A. Vitale A. Boccagni P. Brolese A. Neri D. Srsen N. Gringeri E. Valmasoni M. D'Amico F. Ciarleglio F.A. Violi P. Bonsignore P. Pauletto A. Bassi D. D'Amico Jr. F. Burra P. Masier A. Rigotti P. Furian L. Polacco M. D'Amico D.F. Cillo U. Transplantation Proceedings (2007) 39:6 (1933-1935). Date of Publication: July/August 2007 | Excluded, not pertinent to query search |
| 750. Early virological response in children with chronic hepatitis C treated with pegylated interferon and ribavirin Kowala-Piaskowska A. Słuzewski W. Figlerowicz M. Mozer-Lisewska I. Infection (2007) 35:3 (175-179). Date of Publication: June 2007 | Excluded, incomplete data (only EVR provided) |
| 751. Acute exacerbation of hepatitis in a boy with chronic HCV genotype-2 infection after a 9-year period of normal transaminases levels Tajiri H. Etani Y. Mushiake S. Hasegawa Y. Ozono K. European Journal of Pediatrics (2007) 166:5 (501-502). Date of Publication: May 2007 | Excluded, not pertinent to query search |
| 752. Presence of hepatitis C virus (HCV)-RNA in peripheral blood mononuclear cells in HCV serum negative patients during interferon and ribavirin therapy Januszkiewicz-Lewandowska D. Wysocki J. Pernak M. Nowicka K. Zawada M. Rembowska J. Lewandowski K. Mańkowski P. Nowak J. Japanese Journal of Infectious Diseases (2007) 60:1 (29-32). Date of Publication: 2007 | Excluded, not pertinent to query search |
| 753. Interferon alfa-2b and ribavirin. In children: More risks than in adults Prescrire International (2007) 16:88 (63-65). Date of Publication: April 2007 | Excluded, not pertinent to query search |
| 754. Recommendations for the treatment of chronic hepatitis B infection in children Shah U. Memon I. Cheema H.A. Ali S. Thobani S. Mirza R. Journal of the Pakistan Medical Association (2007) 57:4 (204-207). Date of Publication: April 2007 | Excluded, not pertinent to query search |
| 755. A randomised study of peginterferon and ribavirin for 16 versus 24 weeks in patients with genotype 2 chronic hepatitis C Yu M.-L. Dai C.-Y. Huang J.-F. Hou N.-J. Lee L.-P. Hsieh M.-Y. Chiu C.-F. Lin Z.-Y. Chen S.-C. Hsieh M.-Y. Wang L.-Y. Chang W.-Y. Chuang W.-L. Gut (2007) 56:4 (553-559). Date of Publication: April 2007 | Excluded, not pertinent to query search |
| 756. Significance of blood analysis in hemophiliacs co-infected with human immunodeficiency virus and hepatitis viruses Shen F. Huang Q. Sun H.-Q. Ghildyal R. World Journal of Gastroenterology (2007) 13:12 (1862-1866). Date of Publication: 28 Mar 2007 | Excluded, not pertinent to query search |
| 757. Modulation of the IL-12/IFN-γ axis by IFN-α therapy for hepatitis C Byrnes A.A. Li D.-Y. Park K. Thompson D. Mocilnikar C. Mohan P. Molleston J.P. Narkewicz M. Zhou H. Wolf S.F. Schwarz K.B. Karp C.L. Journal of Leukocyte Biology (2007) 81:3 (825-834). Date of Publication: 1 Mar 2007 | Excluded, not pertinent to query search |
| 758. Hepatitis C virus genotypes among patients with thalassemia and inherited bleeding disorders in Markazi province, Iran Samimi-Rad K. Shahbaz B. Haemophilia (2007) 13:2 (156-163). Date of Publication: March 2007 | Excluded, not pertinent to query search |
| 759. Fibrosis progression in hepatitis C positive liver recipients after sustained virologic response to antiviral combination therapy (interferon-ribavirin therapy) Bahra M. Neumann U.P. Jacob D. Langrehr J.M. Berg T. Neuhaus R. Neuhaus P. Transplantation (2007) 83:3 (351-353). Date of Publication: February 2007 | Excluded, not pertinent to query search |
| 760. Clinical Spectrum and Histopathologic Features of Chronic Hepatitis C Infection in Children Mohan P. Colvin C. Glymph C. Chandra R.R. Kleiner D.E. Patel K.M. Luban N.L.C. Alter H.J. Journal of Pediatrics (2007) 150:2 (168-174.e1). Date of Publication: February 2007 | Excluded, not pertinent to query search |
| 761. Factors influencing the progression of fibrosis in patients with recurrent hepatitis C after liver transplantation under antiviral therapy: A retrospective analysis of 939 liver biopsies in a single center Walter T. Dumortier J. Guillaud O. Hervieu V. Scoazec J.-Y. Boillot O. Liver Transplantation (2007) 13:2 (294-301). Date of Publication: February 2007 | Excluded, not pertinent to query search |
| 762. Discordant outcome of perinatal transmission of hepatitis C in twin pregnancies Boxall E. Baumann K. Price N. Sira J. Brown M. Kelly D. Journal of Clinical Virology (2007) 38:2 (91-95). Date of Publication: February 2007 | Excluded, not pertinent to query search |
| 763. Prevalence of hepatitis C in a German prison for young men in relation to country of birth Meyer M.F. Wedemeyer H. Monazahian M. Dressman J. Manns M.P. Lehmann M. Epidemiology and Infection (2007) 135:2 (274-280). Date of Publication: February 2007 | Excluded, not pertinent to query search |
| 764. NF1 plexiform neurofibroma growth rate by volumetric MRI: Relationship to age and body weight Dombi E. Solomon J. Gillespie A.J. Fox E. Balis F.M. Patronas N. Korf B.R. Babovic-Vuksanovic D. Packer R.J. Belasco J. Goldman S. Jakacki R. Kieran M. Steinberg S.M. Widemann B.C. Neurology (2007) 68:9 (643-647). Date of Publication: February 2007 | Excluded, not pertinent to query search |
| 765. Response to pegylated interferon α-2b and ribavirin in children with chronic hepatitis C Baker R.D. Dee D. Baker S.S. Journal of Clinical Gastroenterology (2007) 41:1 (111-114). Date of Publication: January 2007 | Excluded, not satisfying eligibility criteria (retrospective study) |
| 766. Amino acid substitutions in the hepatitis C virus core region are the important predictor of hepatocarcinogenesis Akuta N. Suzuki F. Kawamura Y. Yatsuji H. Sezaki H. Suzuki Y. Hosaka T. Kobayashi M. Kobayashi M. Arase Y. Ikeda K. Kumada H. Hepatology (2007) 46:5 (1357-1364). Date of Publication: 2007 | Excluded, not pertinent to query search |
| 767. Rejection under alpha interferon therapy in liver transplant recipients Walter T. Dumortier J. Guillaud O. Hervieu V. Paliard P. Scoazec J.-Y. Boillot O. American Journal of Transplantation (2007) 7:1 (177-184). Date of Publication: January 2007 | Excluded, not pertinent to query search |

## Appendix 4. Results of the abstracts search among the proceedings of the 2015 to 2017 annual meetings of the European Association for the Study of Liver Disease, American Association for the Study of Liver Disease, European Society of Pediatric Gastroenterology, Hepatology and Nutrition, North American Society of Pediatric Gastroenterology, Hepatology and Nutrition and of the European Society of Pediatric Infectious Disease

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| --- | --- | --- |
| **No and reference** | **Excluded / included and main reason for exclusion** | **Clinicaltrial.gov accession number** |
| 1. Kirby B, German P, Kanwar B, Ni L, Lakatos I, Ling J, Mathias A. Pharmacokinetics of Once Daily Sofosbuvir or Ledipasvir/Sofosbuvir in HCV-Infected Adolescents. Hepatology 2015;62 (S1): abstract 1707. | Excluded, reporting mainly on pharmacokinetics | NCT 02249182 and NCT 02175758 |
| 2. Schwarz K, Murray KF, Rosenthal P, Bansal S, Lin CH, Ni L, Kanwar B, Fraser J, German P, Brainard DM, Wen J, Gonzalez-Peralta R, Jonas MM, Balistreri W. High rates of SVR12 in adolescents treated with the combination of ledipasvir/sofosbuvir. J Hepatol 2016;64 (S2): abstract GS17. | Excluded duplicate publication | NCT 02249182 |
| 3. Balistreri W, Rosenthal P, Bansal S, Gonzalez-Peralta R, Wen J, Whitworth MS, Lin C-H, Jonas MM, Rodriguez-Baez N, Kanwar B, Brandt-Sarif T, Zhu Y, German P, Kersey K, Brainard DM, Schwarz K, Murray KF. Ledipasvir/sofosbuvir for 12 weeks is safe and effective in adolescents with chronic hepatitis C infection. J Pediatr Gastroenterol Nutr 2016;63(S2):S140-S141. A 420 | Excluded, duplicate publication | NCT 02249182 |
| 4. Cheema HA, Hashmi A. Efficacy and safety of sofosbuvir in hepatitis c infection in children. J Pediatr Gastroenterol Nutr 2016;63(S2):S140-S141. A600 | Excluded, non controlled trial |  |
| 5. Garrison KL, Mathias A, Kersey K, Kanwar B, Ni L, Jain A, Ling J, Gonzalez-Peralta RP, Murray KF, Lin CH, Whitworth MS, Wen J, Schwarz KB, Balistreri W. Pharmacokinetics of Once Daily Sofosbuvir or Ledipasvir/Sofosbuvir in HCV-Infected Pediatrics Aged 6 to <12 Years Old. Hepatology 2016;64(S1):abstract 878 | Excluded, reporting mainly on pharmacokinetics | NCT 02249182 and NCT 02175758 |
| 6. Schwarz KB, Rosenthal P, Gonzalez-Peralta RP, Jonas MM, Balistreri W, Lin CH, Hardikar W, Kersey K, Kanwar B, Brainard DM, Massetto B, Zhu Y, Prasse A, Kirby B, Arnon R, Murray KF, Wirth S. Sofosbuvir + Ribavirin for 12 or 24 Weeks Is Safe and Effective in Adolescents with Genotype 2 or Genotype 3 Chronic Hepatitis C Infection. Hepatology 2016;64(S1):abstract 706. | Excluded, duplicate publication | NCT 02175758 |
| 7. Murray KF, Balistreri W, Bansal S, Whitworth S, Evans H, Gonzalez-Peralta RP, Wen J, Massetto B, Kersey K, Zhu Y, GarrisonK, Svarovskaia E, Brainard DM, Arnon R, Gillis L, Jonas MM, Lin CH, Narkewicz MR, Schwarz K, Rosenthal P. 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(1):PS101. | Included | NCT 02249182 |
| 8. Younossi ZM, Stepanova M, Balistreri W, Schwarz KB, Murray KF, Rosenthal P, Bansal S, Hunt S. High Efficacy and Significant Improvement of Quality of Life (QoL) in Adolescent Patients with Hepatitis C Genotype 1 (GT1) Treated with Sofosbuvir (SOF) and Ledipasvir (LDV). Hepatology 2016;64(S1): A709 | Excluded, reporting mainly on quality of life and duplicate results | NCT 02249182 |
| 9. Leung DH, Yao B, Viani RM, Gonzalez-Peralta RP, Jonas MM, Lobritto SJ, Narkewicz MR, Sokal E, Fortuny C, Hsu E, Wirth S, Del Valle-Segarra A, Zha J, Larsen L, Liu L, Shuster DL, Cohen DE, Rosenthal P. ZIRCON: pharmacokinetics, safety, and efficacy of ombitasvir/paritaprevir/ritonavir ± dasabuvir ± ribavirin in adolescents with genotype 1 or 4 hepatitis C virus infection. J Hepatol 2017;66(1):THU-251 | Included | NCT 02486406 |
| 10. El-Sayed M, Hassany M, Asem N. 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(1):THU-412. | Included | NCT 02868242 |
| 11. Leung D, Yao B, Viani R, Gonzalez-Peralta R, Jonas M, Lobritto S, Narkewicz M, Sokal E, Fortuny C, Hsu E, Wirth S, Del Valle-Segarra A, Zha J, Larsen L, Liu L, Shuster D, Cohen D, Rosenthal P. Pharmacokinetics, safety and efficacy of ombitasvir/paritaprevir/ritonavir ± dasabuvir ± ribavirin in hepatitis C genotype 1 or 4 virus infected adolescents: the zircon study. 2017 Annual Meeting of the European Society of Pediatric Infectious Disease. Abstract ESP17-1125 | Excluded, duplicate publication | NCT 02486406 |

## Appendix 5. Additional non duplicate publications added using bibliography searches

|  |  |
| --- | --- |
| **No and reference** | **Excluded / included and main reason for exclusion** |
| 1. Wirth S, Pieper-Boustani H, Lang T, Ballauff A, Kullmer U, Gerner P, Wintermeyer P, Jenke A. Peginterferon alfa-2b plus ribavirin treatment in children and adolescents with chronic hepatitis C. Hepatology. 2005 May;41(5):1013-8. | Included |
| Balistreri WF, Murray KF, Rosenthal P, Bansal S, Lin CH, Kersey K, Massetto B, Zhu Y, Kanwar B, German P, Svarovskaia E, Brainard DM, Wen J, Gonzalez-Peralta RP, Jonas MM, Schwarz K. The safety and effectiveness of ledipasvir-sofosbuvir in adolescents 12-17 years old with hepatitis C virus genotype 1 infection. Hepatology. 2016 Dec 20. doi: 10.1002/hep.28995 | Included |
| Wirth S, Rosenthal P, Gonzalez-Peralta RP, Jonas MM, Balistreri WF, Chuan-Hao L, Hardikar W, Kersey K, Massetto B, Kanwar B, Brainard DM, Shao J, Svarovskaia E, Kirby B, Arnon R, Murray KF, Schwarz KB. Sofosbuvir and Ribavirin in Adolescents 12 to 17 Years Old With Hepatitis C Virus Genotype 2 or 3 Infection. Hepatology. 2017 | Included |

## Table B. Summary of the data of interest reported in the clinical trials using pegylated interferon and ribavirin included in the systematic review

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Study** | **Al Ali 2010(1)** | **El-Karaksy 2016(2)** | **Indolfi 2016(3)** | **Jara 2008(4)** | **Megahed 2017(5)** | **Pawlowska 2010(6)** | **Schwarz 2011(7)** | **Shaker 2013(8)** | **Sokal 2010(9)** | **Wirth 2005(10)** | **Wirth 2010(11)** |
| type of PEG IFN | α-2b |  | α-2b | α-2b | α-2b | α-2b | α-2a | α-2b | α-2a | α-2b | α-2b |
| dose of PEG IFN (per week) | 1.5 μg/Kg | 1.5 μg/Kg | 1.5 µg/Kg | 1 μg/Kg | 1.5 μg/Kg | 1.5 μg/Kg | 180 μg/1.73  m2 | 60 μg/m2 | 100 μg/m2 | 1.5 μg/Kg | 60 μg/m2 |
| n | 12 | 66 | 64 | 30 | 46 | 53 | 55 | 33 | 65 | 53 | 107 |
| GT 1 and 4 | 12 (100) | 66 (100) | 26 (40.6) | 27 (90) | 46 | 51 (96.2) | 45 (81.2) | 33 (100) | 47c (72.3) | 48 (90.6) | 77 (71.9) |
| GT 2 and 3 | 0 | 0 | 38 (59.4) | 3 (10) | 0 | 2 (3.8) | 10 (18.8) | 0 | 18 (27.7) | 5a (9.4) | 30 (28.1) |
| SVR |  |  |  |  |  |  |  |  |  |  |  |
| GT 1 and 4 | 9/12 (75) | 28/66 (42.4) | 14/26 (53.8) | 11/27 (40.7) | 23/46 (50) | 25/51 (49) | 21/45 (47) | 11/33 (33.3) | 27/47 (57) | 23/48 (47.9) | 42/77 (54.5) |
| GT 2 and 3 | 0 | 0 | 37/38 (97.4) | 3/3 (100) | 0 | 1/2 (50) | 8/10 (80) | 0 | 16/18 (89) | 5/5 (100) | 28/30 (93) |
| relapse | 1/12 (8.3) | 1/66 (1.5) | 1/64 (1.6) | 1/30 (3.3) | 1/46 (2.1) | 9/53 (16.9) | 9/55 (16.4) | NR | 0 | 4/53 (7.5) | 9/107 (8.4) |
| virologic breakthrough | 0 | 0 | 1/64 (1.6) | 2/30 (6.7) | 1/46 (2.1) | 6/53 (11.3) | NR | NR | 0 | 6/53 (11.3) | NR |
| treatment discontinuations | 1/12 (8.3) | 37/66 (56) | 12/64 (18.7) | 13/30 (43.3) | 4/46 (8.7) | 0 | NR | 0 | 10/65 (15.4) | 19/53 (35.8) | NR |
| lack of virologic response | 0 | 36/66 (54.5) | 12/64 (18.7) | 10/30 (33.3) | 4/46 (8.7) | 0b | NR | 0 | 8/65 (12.3) | 18/53 (33.9) | NR |
| adverse event | 1/12 (8.3) | 1/66 (1.5) | 0 | 3/30 (10) | 0 | 0 | 4/55 (7.3) | 0 | 2/65 (3) | 1/53 (1.8) | 1/107 (0.9) |

Note: PEG IFN, pegylated interferon; ribavirin was used at the standard dose 15 mg/Kg/daily in two divided doses. aonly data from children treated for 24 weeks were presented; bno discontinuation rule due to a lack of virological response was applied; c1 patient with HCV genotype 5 infection. Values between brackets: percent of total.

## Table C. Summary of the data of interest reported in the clinical trials using direct acting antiviral included in the systematic review.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Study** | **Balistreri 2017(12)** | **Wirth 2017(13)** | **Murray 2017(14)** | **Leung 2017(15)** | **El-Sayed 2017(16)** |
|  | ledipasvir/sofosbuvir ± ribavirin | sofosbuvir + ribavirin | ledipasvir/sofosbuvir | ombitasvir/paritaprevir/ritonavir ± dasabuvir ± ribavirin | sofosbuvir + daclatasvir ± ribavirin |
| dose (mg) | 90/400 | 400 + 15 per Kg | 45/200 | 150/100/25 + 250 + 15 per Kg | 400 + 60 + 15 per Kg |
| age (yr) | 12-17 | 12-17 | 6-11 | 12-17 | 12-17 |
| n | 100 | 52 | 90 | 38 | 13 |
| GT 1 and 4 | 100 (100) | 0 | 88 (97.8) | 38 (100) | 13 (100) |
| GT 2 and 3 | 0 | 52 (100) | 2 (2.2) | 0 | 0 |
| SVR |  |  |  |  |  |
| GT 1 and 4 | 98/100 (98)b | 0 | 87/88 (98.9) | 38/38 (100) | 13/13 (100) |
| GT 2 and 3 | 0 | 51/52 (98)a | 2/2 (100) | 0 | 0 |
| relapse | 0 | 0 | 1/90 (1.1) | 0 | 0 |
| virologic breakthrough | 0 | 0 | 0 | 0 | 0 |
| treatment discontinuations | 0 | 0 | 0 | 0 | 0 |
| lack of virologic response | 0 | 0 | 0 | 0 | 0 |
| adverse event | 0 | 0 | 0 | 0 | 0 |

aone patient did not achieve SVR12 was lost to follow-up after achieving SVR4; b 2 patients who did not achieve SVR12 were lost to follow-up either during or after

treatment. Values between brackets: percent of total.

**References**

1. Al Ali J, Owayed S, Al-Qabandi W, 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.

2. El-Karaksy HM, Sharaf SA, Mandour IA, 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.

3. Indolfi G, Nebbia G, Cananzi M, et al. Kinetic of Virologic Response to Pegylated Interferon and Ribavirin in Children With Chronic Hepatitis C Predicts the Effect of Treatment. Pediatr Infect Dis J 2016;35:1300-3.

4. Jara P, Hierro L, de la Vega A, 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.

5. Megahed A, Salem N, Fathy A, et al. Pegylated interferon alpha/ribavirin therapy enhances bone mineral density in children with chronic genotype 4 HCV infection. World J Pediatr 2017 in press.

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