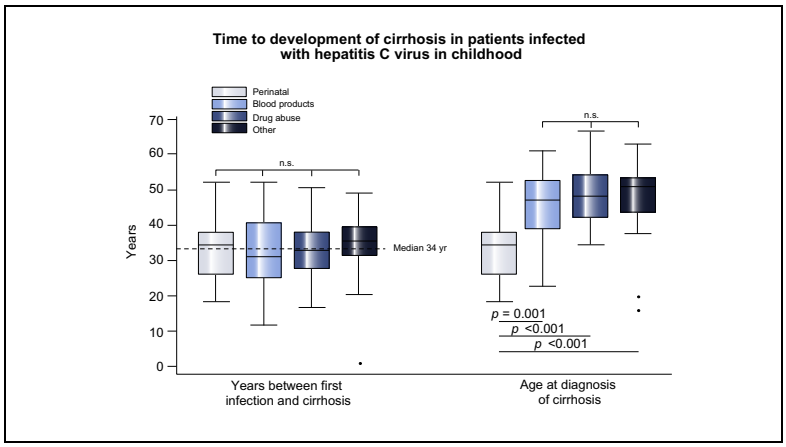
Research Article
Viral Hepatitis

JOURNAL
OF HEPATOLOGY

Epidemiology and natural history of hepatitis C virus infection among children and young people

Graphical abstract



Highlights

- In UK children, HCV infection is transmitted by IV drug use in 53%, blood products in 24% and perinatally in 11%.
- Cirrhosis occurs in 32% of patients, a median of 33 years after infection, irrespective of infection route.
- Treatment impact on disease progression better if started before cirrhosis.
- Anti-HCV therapy should be available in childhood to prevent long-term liver disease.

Authors

Line Modin, Adam Arshad, Bryony Wilkes, ..., Carla Lloyd, William L. Irving, Deirdre A. Kelly

Correspondence

line.modin@nhs.net
(L. Modin)

Lay summary

Chronic hepatitis C virus (HCV) infection is a global health problem, which can now be treated with potent direct-acting antiviral drugs. This study demonstrates that HCV infection in childhood causes serious liver disease in 32% of patients, a median of 33 years after infection, irrespective of age, mode and route of infection. Disease outcomes were better in patients treated before the development of advanced liver disease. Antiviral therapy should be made available in childhood to prevent long-term liver disease and the spread of HCV.

http://dx.doi.org/10.1016/j.jhep.2018.11.013
© 2018 European Association for the Study of the Liver. Published by Elsevier B.V. All rights reserved. J. Hepatol. 2019, 70, 371–378

Research Article
Viral Hepatitis

JOURNAL OF HEPATOLOGY

Epidemiology and natural history of hepatitis C virus infection among children and young people

Line Modin[1,*], Adam Arshad[1], Bryony Wilkes[2], Jennifer Benselin[2], Carla Lloyd[1], William L. Irving[2], Deirdre A. Kelly[1]

[1]*Liver Unit, Birmingham Women's & Children's Hospital, Birmingham, UK;* [2]*Gastrointestinal and Liver Disorders Team, NIHR Nottingham Biomedical Research Centre, Nottingham University Hospital NHS Trust and the University of Nottingham, UK*

Background & Aims: Chronic hepatitis C virus (HCV) infection is a global health burden. Although HCV infection rarely contributes to morbidity during childhood, most HCV-infected children develop chronic HCV with a lifetime risk of liver disease. Little is known about the development of long-term liver disease and the effect of treatment in patients infected with HCV in childhood.

Method: This study was a retrospective review of patients infected with HCV in childhood enrolled in HCV Research UK. A total of 1,049 patients were identified and included.

Results: The main routes of infection were intravenous drug use (53%), blood product exposure (24%) and perinatal infection (11%). Liver disease developed in 32% of patients, a median of 33 years after infection, irrespective of the mode of infection. Therefore, patients with perinatal exposure developed cirrhosis at an earlier age than the rest of the risk groups. The incidence of hepatocellular carcinoma (HCC) was 5%, liver transplant 4% and death occurred in 3%. Overall, 663 patients were treated (55% with interferon/pegylated interferon and 40% with direct-acting antivirals). Sustained virological response (SVR) was achieved in 406 (75%). There was a higher mortality rate among patients without SVR *vs.* those with SVR (5% *vs.* 1%, $p = 0.003$). Treatment was more effective in patients without cirrhosis and disease progression was less frequent (13%) than in patients with cirrhosis at the time of therapy (28%) $p < 0.001$. Patients with cirrhosis were more likely to develop HCC, require liver transplantation, or die.

Conclusion: HCV infection in young people causes significant liver disease, which can now be prevented with antiviral therapy. Early treatment, especially before development of cirrhosis is essential. Detection of HCV should be aimed at relevant risk groups and antiviral therapy should be made available in childhood to prevent long-term liver disease and spread of HCV.

Lay summary: Chronic hepatitis C virus (HCV) infection is a global health problem, which can now be treated with potent direct-acting antiviral drugs. This study demonstrates that HCV infection in childhood causes serious liver disease in 32% of patients, a median of 33 years after infection, irrespective of age, mode and route of infection. Disease outcomes were better in patients treated before the development of advanced liver disease. Antiviral therapy should be made available in childhood to prevent long-term liver disease and the spread of HCV.

© 2018 European Association for the Study of the Liver. Published by Elsevier B.V. All rights reserved.

Introduction

Chronic hepatitis C virus (HCV) infection is a global health burden with an estimated prevalence varying between 0.6%–10% dependent on geographical location and an estimated 71 million people worldwide with chronic infection.[1–3] In Western Europe, the estimated prevalence is 1.5%–3.5%, but in the UK it is 0.5%. Chronic HCV is associated with increased morbidity and mortality and is a leading cause of end-stage liver disease, cirrhosis and liver cancer worldwide.[3–6] Although HCV infection rarely contributes to morbidity during childhood, the majority of HCV-infected children develop chronic HCV with a lifetime risk of serious liver disease.[7] Furthermore, some studies indicate that HCV affects childhood quality of life and behaviour, as cognitive function has been shown to be affected and families report increased stress which affects family dynamics and wellbeing.[7,8]

Several factors have been associated with accelerated disease progression, but it is not clear whether or not infection in early life carries a different risk of progressive disease than infection in adulthood.[9,10] Since the mode of infection and genotype differs between countries and regions, knowledge of epidemiology at a local level is important in order to effectively plan prevention, surveillance, and prioritise treatment.[11] Currently, there are few data on mode of infection, genotype and development of long-term liver disease in patients infected with HCV in childhood in the UK.

Currently, access to clinical trials of direct-acting antivirals (DAAs) in childhood is limited which denies timely access to effective therapies for young infected children. HCV Research UK is a UK database and biobank which established a cohort of HCV-infected children and adults to address gaps in knowledge of epidemiology, treatment, disease progression, and prognosis.[12,13]

The aim of this study was to describe the epidemiology and natural history of HCV in a UK cohort of patients who were infected during childhood.

Keywords: Child; Chronic hepatitis; Hepatocellular carcinoma; Liver cirrhosis; Viral hepatitis.
Received 7 June 2018; received in revised form 16 October 2018; accepted 10 November 2018; available online 27 November 2018
* Corresponding author. Address: Liver Unit, Birmingham Women's & Children's Hospital, Steelhouse Lane, Birmingham B4 6NH, UK. Tel.: +44 7445050231.
E-mail address: line.modin@nhs.net (L. Modin).

Patients and methods

This was a retrospective, descriptive study of patients infected with HCV in childhood in the UK.

The HCV Research UK database and biobank

HCV Research UK is a national, clinical, multicentre research database and biobank set up in 2012 to collect information about adults and children infected with HCV in the UK.[12,13] All highly populated areas of the UK are represented in the cohort and only patients who were in prison at time of clinic appointments or patients who were unable to give written informed consent were excluded from recruitment. More than 10,000 patients with past or current infection have been enrolled from 51 specialist adult and 7 paediatric HCV centres. Written informed consent was obtained at time of enrolment. For children under 16 years, this was supplied by parents or legal guardians. The HCV Research UK database holds anonymised information including demographic data, risk factors for HCV infection including date of first exposure to risk, past and current alcohol intake, virology data, laboratory data, biopsy and imaging results.[13] The baseline data at enrolment of each participant is collected through a detailed, standardised questionnaire while follow-up data is collected through assessment of medical notes. In addition, prospective clinical data on risk behaviours, physical characteristics, HCV virology, comorbidities, liver disease status, treatment, and mortality are collected biennially for all patients in the cohort.

Diagnosis of cirrhosis was made at the discretion of the local physician by histology, imaging studies, serum markers or clinical diagnosis with accompanying clinical signs (ascites, portal hypertension, and/or variceal bleed).

Patients

Clinical and epidemiological data from patients enrolled in the HCV Research UK clinical database and biobank was requested in October 2016 and the data updated in March 2017. Patients were included if age at first infection was estimated (based on first exposure to risk) to be between 0–18 years or if age between 0–18 years was recorded at the time of first positive HCV test, the time of first attendance or at the time of consent.

Statistical analysis

Statistical analyses were performed using STATA 13 (StataCorp LP, Texas). Clinical characteristics were analysed in a descriptive way and reported as mean ± SD or median and range where assumptions of normal distribution were not met. For pairwise comparison, chi-square test was used for binary outcome variables and Fisher exact test was used for small samples.

The unpaired *t* test and multivariate logistic regression with indicator variable was used for continuous numerical outcome variables and Wilcoxon rank-sum test was used for non-normally distributed data. Statistical significance was defined as $p < 0.05$.

Results

Demographic data

In total, 1,086 patients infected with HCV in childhood were identified from the HCV Research UK database of whom 37 patients were excluded due to discrepancies between date of birth, date of infection and possible infection route leaving 1,049 patients for data analysis. The estimated time of first infection between 0 and 18 years was given in 984/1,049 (94%) of patients, while the remaining 65 patients were included based on age <18 years at their first positive HCV test (n = 64) or their age at consent <18 years (n = 1). Baseline characteristics of the cohort are provided (Table 1).

HCV genotypes, tested in 938 patients (89%), were G1: 531 (57%); G2: 50 (5%); G3: 328 (35%), G4: 27 (3%), G5: 1 (0.1%) and mixed type: 1 (0.1%). Forty-four (4%) patients were coinfected with human immunodeficiency virus (HIV) of whom 41 (93%) were treated with antiretrovirals; 363 (35%) had a history of heavy alcohol use, 301/759 (40%) males and 62/287 (22%) females, $p < 0.001$. Spontaneous clearance of infection was seen in 3% (36/1,049), of whom 26 (72%) were males.

Route of infection

Patient characteristics by mode of infection are provided (Table 2). The most prevalent route of infection was intravenous drug use (IVD group): 560 (53%), followed by receipt of blood products (blood group): 251 (24%), including 85 with coagulation bleeding disorders; perinatal exposure (perinatal group): 119 (11%) and unknown or other route of infection (unknown group): 119 (11%). There were less male patients in the perinatal group (35%) compared to the IVD blood and other infection route groups (78%, 77% and 73% respectively, $p < 0.001$). The genotype distribution shows fewer genotype 3 infections in

Table 1. Patient characteristics of 1,049 patients enrolled in the HCV Research UK project between March 2012 and October 2016.

Demographic variable	Result	n
Male	759 (72.3)	1,046[1]
Age at infection, median (range)	15 (0–18)	1,049
Age at first positive HCV test, median (range)	33 (0–65)	1,049
Current age, median (range)	50 (3–77)	1,049
Ethnicity		
White	945 (90.9)	1,040[2]
Asian	52 (5.0)	1,040[2]
African	12 (1.2)	1,040[2]
Arabic	8 (0.8)	1,040[2]
Other	23 (2.2)	1,040[2]
Infection route		
Intravenous drug use	560 (53.4)	1,049
Transfusion of blood/blood products	251 (23.9)	1,049
Vertical transmission	119 (11.4)	1,049
Other or unknown transmission route[3]	119 (11.4)	1,049
Genotype		
1	531 (56.6)	938[4]
2	50 (5.3)	938[4]
3	328 (35)	938[4]
4	27 (2.9)	938[4]
5	1 (0.1)	938[4]
Mixed	1 (0.1)	938[4]
Risk factor for infection		
Coagulation bleeding disorder[5]	85 (8.2)	1,032[5]
Co-factors for disease progression		
HIV coinfection	44 (4.4)	998[6]
History of heavy alcohol use	363 (35.3)	1,029[7]

Data in the Table are presented as n (%), unless otherwise specified. HCV, Hepatitis C virus, HIV, human immunodeficiency virus.
[1] Missing: 3.
[2] Missing: 9.
[3] Including tattoos, dental work, born abroad, surgery, and unknown.
[4] Missing/unknown: 111.
[5] Haemophilia, idiopathic thrombocytopenic purpura, Von Willebrands, thalassemia, missing: 17.
[6] Missing/not tested: 51.
[7] Missing: 20.

Table 2. Patient characteristics and development of liver disease in 1,049 patients diagnosed with hepatitis C in childhood by mode of infection.

Demographic variable	Infection route			
	Perinatal group (n = 119)	Blood group (n = 251)	IV group (n = 560)[1]	Unknown group (n = 119)
Male	42 (35)	194 (77)	434 (78)	87 (73)
Age at first infection, years, median (range)	0 (0–1)	11 (0–17)	16 (10–18)	15 (0–18)
Age at first positive HCV test, years, median (range)	2 (0–53)[2]	29 (0–64)	38 (12–65)	37 (3–65)
Years between first infection and diagnosis, years, median (range)	2 (0–53)	19 (0–52)	22 (0–51)	24 (0–50)
Current age years, median (range)	14 (3–55)	48 (21–73)	52 (21–77)	52 (10–72)
Follow-up time, years, median (range)	13 (3–55)	36 (8–59)	37 (5–61)	37 (4–57)
Genotype				
1	59 (50)	159 (64)	257 (46)	56 (47)
2	1 (1)	9 (4)	34 (6)	6 (5)
3	42 (35)	46 (18)	198 (35)	42 (35)
4 and 5	6 (5)	9 (4)	10 (2)	3 (3)
Mixed type	–	–	–	1 (1)
Unknown	11 (9)	28 (10)	61 (11)	11 (9)
Risk factors for disease progression				
History of heavy alcohol use	2 (2)	39 (16)	279 (50)	43 (36)
IV drug use within the last 6 months	–	–	45 (8)	1[2] (0.8)
Development of liver disease				
Cirrhosis	10 (8)	79 (32)	205 (37)	40 (34)
Age at cirrhosis, years, median (range)	36 (17–53)	46 (23–61)	48 (33–68)	52 (12–65)
Years between first infection to cirrhosis diagnosis, years, median (range)	36 (17–53)	32 (12–53)	33 (17–51)	36 (1–50)
Hepatocellular carcinoma	–	11 (4)	38 (7)	6 (5)
Age at time of hepatocellular carcinoma, years, median (range)	–	55 (37–63)	56 (48–68)	54 (52–54
Years from first infection to hepatocellular carcinoma, years, median (range)	–	42 (23–53)	40 (32–51)	38 (35–39)
Liver transplant[4]	–	13 (5)	28 (5)	5[3] (4)
Age at time of liver transplant, years, median (range)	–	46 (27–63)	50 (36–66)	51 (4–54)
Years from first infection to liver transplant, years, median (range)	–	37 (16–49)	33 (20–50)	36 (28–39)
Death	–	6 (2)	19 (3)	7 (6)

Data in the Table are presented as n (%), unless otherwise specified. HCV, Hepatitis C virus, HIV, human immunodeficiency virus; IV, intravenous.
[1] One patient was registered in the database with other route of infection (born abroad) and no other risk factor for infection but having IV drug use within the last 6 months.
[2] One patient born in Lithuania was registered in the database with an age of 53 at time of first positive HCV test corresponding to the same year the patient was enrolled in HCV Research UK.
[3] Year 2017 was used to calculate current age when data retrieval was conducted.
[4] One patient has been excluded from transplant data analysis due to transplant on the basis of biliary atresia before the diagnosis of HCV.

the blood group (18%) compared to the other 3 groups (35%) ($p < 0.001$).

Median age at first infection was 16 years (range 10–18) in the IVD group, 11 years (range 0–17) in the blood group and at birth (0 years) in the perinatal group (Fig. 1). The gap between infection and diagnosis was a median 19 to 24 years in the IVD group, blood group and unknown risk group and 2 years in the perinatal group.

Development of liver disease

In total, 334/1,049 (32%) of patients had a diagnosis of cirrhosis at the time of data analysis. Cirrhosis was diagnosed by liver biopsy (110, 33%), imaging studies including transient elastography (85, 25%), endoscopy or clinical signs of cirrhosis (101, 30%), serum markers (7, 2%) and unknown/missing (31, 9%). By multivariate regression analysis, significant risk factors for the development of cirrhosis were male gender (OR 1.6; 95% CI 1.2–2.2; $p = 0.003$) and heavy alcohol use (OR 1.6; 95% CI 1.2–2.8; $p < 0.001$) while HIV coinfection was not significant (OR 0.95; 95% CI −0.2 to 0.5; $p = 0.88$). The time to cirrhosis and age at development of liver disease between the different risk groups is presented, showing that the rate of liver disease progression appears to be similar across all patient groups (Fig. 2).

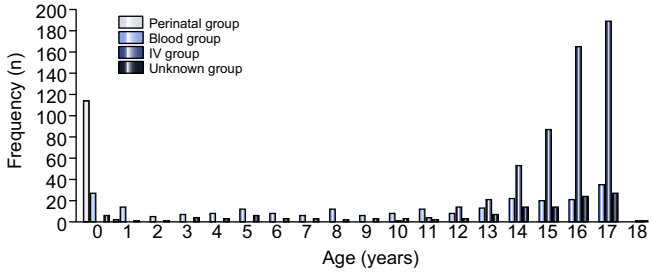


Fig. 1. Patient age at infection by risk group in patients infected with HCV in childhood. HCV, hepatitis C virus; IV, intravenous.

The median time to develop cirrhosis was 33 years (range 12–53) which was estimated in 281/334 (84%) patients. There was no significant difference between any of the groups (IVD group: 33 years; blood group: 32 years; perinatal group 36 years; unknown group: 36 years; $p = 0.76$). Thus, patients with perinatal infection developed cirrhosis earlier at a median age of 36 years (range 17–53) compared to 48 years (range 33–68), 46 years (range 12–61), and 51.5 years (range 12–65) in the IVD, blood, and unknown groups, respectively ($p < 0.001$).

There were less patients with cirrhosis in the perinatal group (8%, 10/119) compared to the IVD, blood and unknown groups (37%, 205/560; 32%, 79/250; 34%, 40/119) ($p < 0.001$). However, 101 (85%) patients with perinatal infection were younger than 33 years of age at the time of data analysis and so may not have

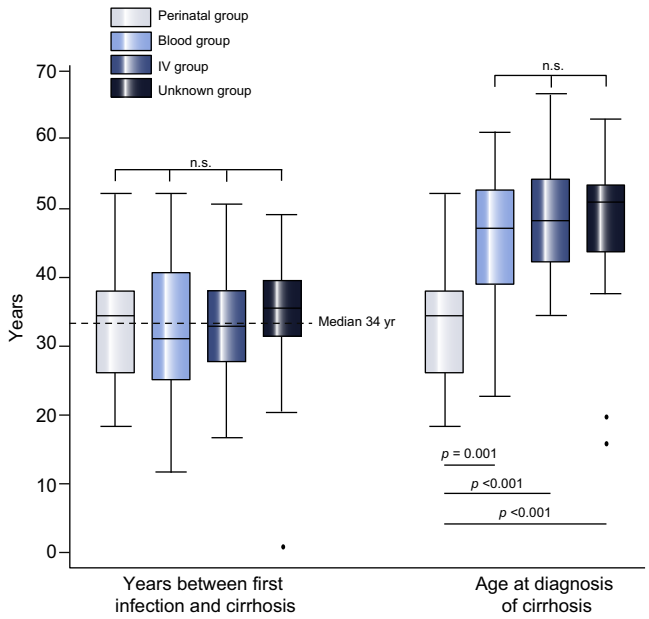


Fig. 2. Time between first infection and diagnosis of cirrhosis and real age in patients infected with HCV in childhood. Multivariate logistic regression with indicator variable, statistical significance was defined as $p < 0.05$. HCV, hepatitis C virus; IV, intravenous.

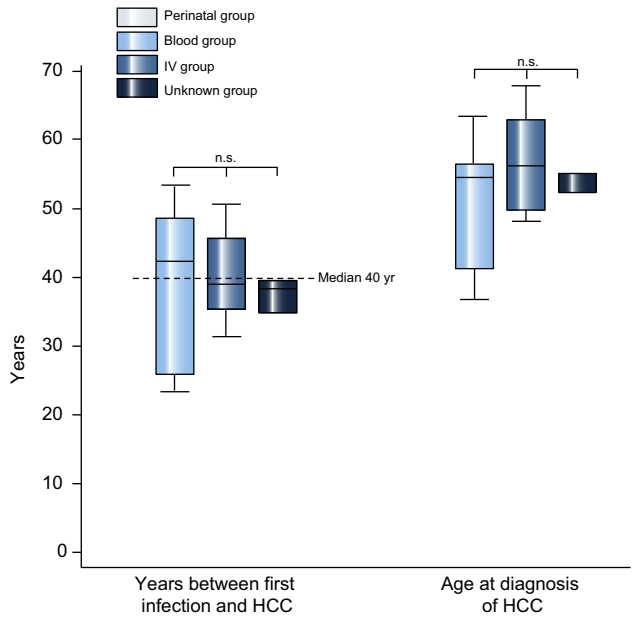


Fig. 3. Time between first infection and diagnosis of hepatocellular carcinoma and real age in patients infected with HCV in childhood. Multivariate logistic regression with indicator variable, statistical significance was defined as $p < 0.05$. HCC, hepatocellular carcinoma; HCV, hepatitis C virus; IV, intravenous.

had time to develop cirrhosis, whilst 7 of the 18 (38%) above the age of 33 years had developed cirrhosis, suggesting a similar pattern of development of cirrhosis irrespective of infection route. Cirrhosis developed in the perinatal group despite the low prevalence of associated risk factors (male gender, heavy alcohol use) compared to the IVD group (Table 2).

HCC was diagnosed in 55/1,049 (5%) of the patients. Of these 55 patients 38/55 (70%) were from the IVD group, 11/55 (20%) in the blood product group, and 6/55 (10%) of the patients in the unknown group. Of the 55 patients with HCC, 44 (80%) had cirrhosis prior to the diagnosis of HCC. There was no difference in heavy alcohol use between patients with (23/44, 52%) or without cirrhosis (6/11, 55%), $p = 0.9$ prior to diagnosis of HCC. Overall, median time to development of HCC was 39 years (range 23–53) while median age at diagnosis of HCC was 55 years (range 37–68) (Fig. 3).

A total of 46 (4%) patients received a liver transplant (LTx). Of these, 33 were cirrhotic and 17 had HCC at the time of transplant. Median time to LTx from first infection was 34 years (range 16–50) while the median age at the time of LTx was 49 years (range 27–66) (Fig. 4). There was no significant effect of mode of transmission for either median time to LTx or median age at the time of LTx ($p = 0.90$ and $p = 0.18$, respectively). There was no difference between those who required LTx and those who did not with regard to HIV coinfection (2/47 (4%) *vs.* 42/1,002 (4%), $p = 0.2$) or history of heavy alcohol use (21/47 (44%) *vs.* 342/1002 (34%), $p = 0.1$). Renal failure was reported more frequently in patients who had LTx (4/47 (9%) *vs.* 7/1,002 (0.7%), $p = 0.001$).

The overall mortality in the cohort was 3% (28/1,049). In multivariate analysis the presence of cirrhosis (OR 6.2; 95% CI 2.6–14.7; $p < 0.001$) was the only significant risk factor. Heavy alcohol use (OR 1.5; 95% CI 0.7–3.3; $p = 0.3$), HCC (OR 1.2; 95% CI 0.4–3.9; $p = 0.8$), gender (OR 1.6; 95% CI 0.5–3.3; $p = 0.8$) and LTx (OR 1.0; 95% CI 0.3–3.7; $p = 0.9$) were not associated with mortality.

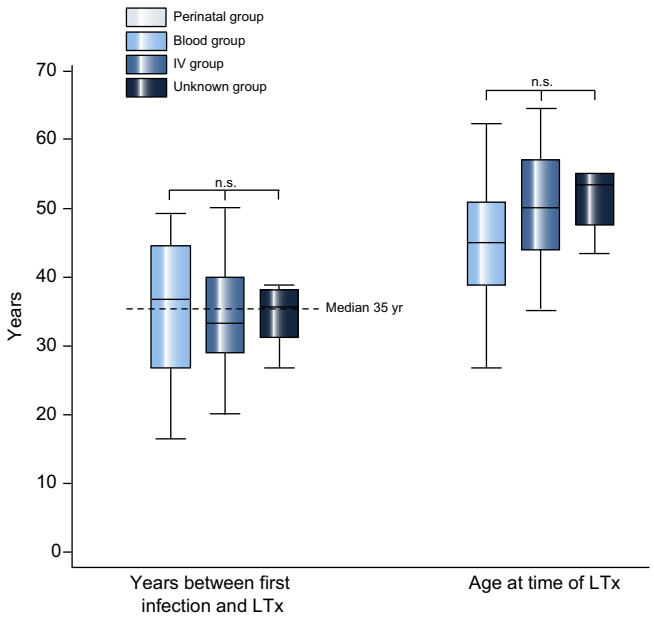


Fig. 4. Time between first infection and time of liver transplantation and real age in patients infected with HCV in childhood. Multivariate logistic regression with indicator variable, statistical significance was defined as $p < 0.05$. HCV, hepatitis C virus; IV, intravenous; LTx, liver transplantation.

Treatment

In total 663 (63%) patients in the cohort had received treatment, 133 and 46 of whom received 2 and 3 separate treatment regimens, respectively. Treatment outcome was missing for 122 individuals. Of the 541 patients whose treatment outcome was known, 292 (54%) received an interferon (IFN)-based treatment regimen + ribavirin (RBV), only 6 patients (1%) received IFN alone, 95 (18%) received IFN in combination with DAAs

Table 3. Treatment outcome according to disease status at onset of therapy and treatment regimen in patients infected with HCV in childhood in whom treatment outcome is known.

Treatment regimen	Non-cirrhotic			Cirrhotic			Cirrhosis status unknown		
	n	SVR	Non-SVR	n	SVR	Non-SVR	n	SVR	Non-SVR
IFN (n = 6)	4 (67%)	2 (50%)	2 (50%)	2 (33%)	2 (100%)	–	–	–	–
IFN + RBV (n = 292)	238 (81%)	162 (68%)	76 (32%)	46 (16%)	32 (70%)	14 (30%)	8 (3%)	6 (75%)	2 (25%)
IFN + DAA (n = 95)	72 (76%)	61 (85%)	11 (15%)	19 (20%)	14 (74%)	5 (26%)	4 (6%)	3 (75%)	1 (25%)
DAA (n = 119)	25 (21%)	22 (88%)	3 (12%)	67 (56%)	56 (84%)	11 (16%)	27 (23%)	21 (78%)	6 (22%)
Unknown (n = 29)	21 (72%)	18 (86%)	3 (14%)	8 (28%)	7 (88%)	1 (12%)	0	0	0
Total (n = 541)	360 (67%)	265 (74%)	95 (26%)	142 (26%)	111 (78%)	31 (22%)	39 (7%)	30 (77%)	9 (23%)

Data is presented as n (%). DAA, direct-acting antiviral; IFN, interferon-based treatment regimen; RBV, ribavirin; SVR, sustained virological response.

and 119 (22%) received DAAs alone. In 29 (5%) patients, the treatment regimen was unknown, mostly because they had taken part in clinical trials. Overall, sustained virological response (SVR) was achieved in 406 (75%) patients while 135 (25%) patients were non-responders or responder-relapsers. Treatment outcomes stratified by the last regimen received and liver disease status are shown in Table 3. There was no difference in the overall SVR rates between non-cirrhotic and cirrhotic patients (265/360 [74%] *vs.* 111/142 [78%]; $p = 0.29$), although this is confounded by the fact that 314/360 (87%) of the former group received an INF-containing regimen, whilst 67/142 (47%) of the latter group received all DAA regimens. The apparently higher SVR rate in cirrhotic patients treated with an interferon-based regimen (32/46, 70%) compared to non-cirrhotic patients (162/238, 68%) was probably caused by the predominance of genotype 3 in the former group (28/46, 61%), as genotype 3 generally responds better to IFN therapies. In the latter group, genotype 1 infections were the most common (115/238, 48%), with only 97 (40%) genotype 3 infections.

Progression of liver disease

A total of 502 patients underwent treatment with complete data (*i.e.* the treatment regimen, outcome and liver disease status were known [142 with cirrhosis and 360 patients without]). The progression of liver disease according to treatment outcome in patients with and without cirrhosis is shown in Table 4.

Disease progression occurred in 87/502 (17%); 47/360 (13%) events were recorded in those without cirrhosis, compared to 40/142 (28%) in patients with cirrhosis ($p < 0.001$). Progression to cirrhosis was seen in 24/265 (9%) patients, who achieved SVR, compared to 15/95 (16%) who failed to achieve an SVR ($p = 0.07$). Progression to HCC, liver transplant or death was seen almost exclusively in those patients who were cirrhotic at treatment onset. Although HCC developed in 16 cirrhotic patients post-SVR, in 12 of these patients, the HCC was diagnosed in the same year that SVR was recorded. It is highly likely, therefore, that many, if not all of these tumours did not arise *de novo* post-SVR in a non-infected liver, but were present during the period of therapy and follow-up to assessment of treatment outcome.

The median length of follow-up for the cirrhotic patients, without further liver disease at time of data analysis was 3 years for those with SVR (range 0–20) and 3 years (range 1–13) for non-SVR patients. For the non-cirrhotic patients, the follow-up time was 5 years (range 1–24) for SVR patients and 6 years (range 1–22) for non-SVR patients.

Significantly more patients with SVR treated with cirrhosis compared to patients treated before diagnosis of cirrhosis progressed to HCC (16 [14%] *vs.* 2 [1%]; $p < 0.001$) or required LTx (7 [6%] *vs.* 3 [1%]; $p = 0.005$) or died (5 [4%] *vs.* 0 [0%]; $p = 0.001$) (Table 4). Furthermore, mortality amongst cirrhotic patients who achieved SVR (5/111, 4%) was significantly less than for those who did not achieve SVR (7/31, 23%, $p = 0.004$).

Table 4. Disease progression according to disease status at onset of therapy and treatment outcome for patients infected with HCV in childhood.

Event		Non-cirrhotic		Cirrhotic	
	Total (n = 502)	SVR (n = 265)	Non-SVR (n = 95)	SVR (n = 111)	Non-SVR (n = 31)
Cirrhosis	39[1] (11%)	24 (9%)	15 (16%)	n.a.	n.a.
HCC	23 (5%)	2[2] (1%)	1 (1%)	16[3] (14%)	4 (13%)
LTx	11 (2%)	3 (1%)	0	7 (6%)	1 (3%)
Death	14 (3%)	0	2[4] (2%)	5[5] (5%)	7[6] (23%)

Data is presented as n (%). HCC, hepatocellular carcinoma; LTx, liver transplantation; SVR, sustained virological response.
[1] This outcome only applies to patients who were non-cirrhotic before therapy, the denominator is 360.
[2] 1 patient also had a liver transplant.
[3] 6 patients also had a liver transplant.
[4] No record of cause of death.
[5] 2 patient had a liver transplant + HCC before death. 2 patients had other cancers, 1 patient with no record of cause of death.
[6] 1 patient had a liver transplant and 1 patient died with HCC, 1 patient had no record of cause of death.

Discussion

This is the first study to describe the epidemiological characteristics and development of long-term liver disease in a UK cohort of patients infected with HCV in childhood. The main route of infection was IV drug use in adolescents in the UK. Serious long-term liver disease developed in one-third of the patients and treatment was more effective in those who were treated before cirrhosis developed, as those treated with cirrhosis were more likely to develop HCC, require liver transplantation, or die. Studies of the development of liver disease in adult patients with chronic HCV prior to treatment have found that alcohol intake and severity of portal fibrosis are correlated with future disease progression and development of cancer.[14] There are few studies describing disease progression in adulthood in patients who were infected with HCV during childhood. Many studies are in heterogeneous populations with insufficient long-term follow-up to provide clear outcomes.[14–17] Previous studies have reported that HCV infection in children differs from adults in some ways such as modes of transmission, rates of clearance, progression of fibrosis, and the duration of potential chronic infection when acquired at birth.[18,19] A risk of the development of hepatic fibrosis whilst in childhood of less than 2% has been reported, but this is much higher in patients with longer follow-up and duration of infection, indicating disease progression is more likely 10 years after the onset of infection.[20–23] Other paediatric studies have demonstrated that the degree of hepatic fibrosis correlates with age and duration of infection and suggest that progression occurs at a slower pace

in young children compared to those infected late in life.[16,24–27] Liver disease may progress more rapidly in older patients because of the presence of multiple additional risk factors such as alcohol consumption and coinfection with HIV, and therefore it is important to distinguish between disease development in those infected as neonates and young people *vs.* disease development in young adults.[18,28–30]

The proportion of HCV-infected children who may develop serious long-term liver disease is not clear from the current literature. In this study 33% of patients infected with HCV in childhood developed long-term liver disease including cirrhosis, HCC or a requirement for LTx. A critical finding in our analysis was that the long-term development of progressive liver disease is independent of the age or route of acquisition, with a median time to diagnosis of 32–36 years. Other studies have suggested that vertically infected children may develop liver disease more frequently than children infected by blood products.[31–33] However, most of these studies do not have data beyond 10 years of follow-up of children infected with HCV and are likely to underestimate the proportion of HCV-infected children who will develop long-term liver disease. Cirrhosis was less frequent in perinatally infected patients compared to the other risk groups in our cohort. However, perinatally infected patients older than 33 years in our cohort had the same frequency of cirrhosis as the other risk groups, even though heavy alcohol use was much less frequent in this subgroup.

The rate of disease progression is influenced by a variety of host, viral, and environmental factors, most notably alcohol abuse and coinfection with hepatitis B virus and HIV.[2,34] Such associations were not evident in our cohort, most likely because of the relatively low frequency of these risk factors in those children infected at an early age.

There was more than a 20 year delay between suspected time of infection and diagnosis of HCV in this cohort, except in the perinatally infected patients, probably because of lack of HCV testing in relevant paediatric risk groups.[9] As all blood donors are now screened for all blood borne viruses, vertical transmission of HCV via mother-to-child transmission is now reported to be the leading cause of paediatric infection globally while risk factors for HCV infection in adults include IVD use, blood transfusion before 1992 and HIV-infection.[35–38]

In this cohort, in contrast to other paediatric studies, more than half of the infected patients reported IV drug use in adolescence as the main route of infection, followed by blood product exposure, while vertical transmission only accounted for 11% of the cases.[39,40] These data reflect the long-term follow-up of this cohort infected with HCV prior to screening of blood products and modern management of IV drug abuse.[41,42] These data may be an underestimate of the actual number of UK children infected with HCV as it is likely that many are not identified and hence are not receiving appropriate treatment and counselling. Healthcare workers at primary and secondary healthcare levels should encourage testing of relevant risk groups, such as young adolescents who participate in IV drug use and the children of such individuals.

Of the patients treated in this cohort, 75% achieved SVR. Life-threatening complications of end-stage liver disease were much less frequent in patients treated before they became cirrhotic (see Table 4) as reported previously in the literature.[43,44]

We have not attempted a more detailed interpretation of the treatment data in this cohort since the data were collected during a period when there were rapid changes in HCV treatment regimens and there are a number of possible confounders. For instance, many of the patients treated with DAAs will be those who had failed earlier treatment regimens and will thus have been a "difficult-to-treat" group, with potentially more severe liver disease at time of initiation of treatment. Nevertheless, our data provide a clear indication of the need to start treatment as early as possible before the development of established liver disease. We have confirmed previous reports that achievement of SVR in patients with cirrhosis reduces, but does not eliminate, the risk of HCC development.[32,33,45]

Some limitations should be considered when interpreting the results. The duration of infection was estimated on the assumption that patients were infected at the time of first exposure to risk. For the IVD group, this is a simplification since it is possible that actual infection occurred sometime later in life. Calculations based on the risk of infection in IVD users suggest that around 50% of all IVD users who acquire HCV infection do so within 3 years of onset of injecting behaviour.[46] Thus, our quoted estimate of time to cirrhosis for this group may be a slight overestimate.

Treatment data from this cohort reflects historical practice as IFN-based treatment regimens are no longer recommended in adult guidelines and DAAs are the preferred treatment with high SVR rates and few side-effects. However, only 2 DAAS are licensed in children over 12 years of age (sofosbuvir with ribavirin and sofosbuvir/ledipasvir). Although clinical trials of DAAs are ongoing in children under 12 years, there will be a delay until they are licensed.[11]

It is likely that we have not enrolled all children with HCV infection in the UK and so there may be selection bias in recruitment of patients who attended specialist clinics, who may have had more severe liver disease.[47] However, we believe the cohort is representative of patients with HCV infection attending specialist treatment centres and therefore an assessment of the long-term outcome of HCV infection in this population. The strengths and limitations of the HCV Research UK cohort are described in more detail elsewhere.[13]

In conclusion, HCV infection in childhood causes serious long-term liver disease which is an important and ongoing problem in the UK which can now be prevented with antiviral therapy. Early treatment, especially before development of cirrhosis, significantly decreases morbidity and mortality associated with HCV infection. We recommend that healthcare workers are aware of the prevalence of HCV in childhood, particularly in young adolescents, and that testing according to NICE guidelines is implemented and treatment is made available. Pharmacological treatment of chronic HCV in childhood should be provided to children by health authorities based on the present evidence of increased risk of serious liver disease in adulthood.

Financial support

Funding to support HCV Research UK was provided by a grant from the Medical Research Foundation, the independent charity of the UK Medical Research Council (award no: C0365).

Conflict of interest

W.L.I. reports grants from Gilead sciences, Abbvie and Bristol Myers Squibb outside the submitted work. D.A.K. and The Liver Unit receive grant funding to perform clinical trials from Roche,

Abbvie and Gilead sciences; D.A.K receives consultancy fees from Roche. All other authors declare no conflicts of interest.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

Study conception and design: AA, WLI, DAK. Data collection: AA, BW, WLI, JB, CL, DAK. Data analysis: LM, WLI, DAK. Draft Manuscript preparation: LM. Final manuscript: All co-authors. All authors had full access to all of the data (including statistical reports and tables) in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Acknowledgements

HCV Research UK investigators are as follows: Agarwal K. (Kings College Hospital, London), Aldersley M. (St James's University Hospital, Leeds), Ala A. (Frimley Park Hospital), Alexander G. (Addenbrookes Hospital, Cambridge), Aspinall R. (Queen Alexandra Hospital, Portsmouth), Barclay S. (Glasgow Royal Infirmary), Barnes E. (John Radcliffe Hospital, Oxford), Bansal S. (King's College Hospital Paediatrics), Bassendine M. (Freeman Hospital, Newcastle), Benselin J. (University of Nottingham), Brown A. (St Mary's Hospital, London), Butterworth J. (Royal Shrewsbury Hospital), Ch'ng C. (Singleton Hospital, Swansea), Cooke G. (St Mary's Hospital, London), Corless L. (Hull Royal Infirmary), Cramp M. (Derriford Hospital, Plymouth), Datta S. (Southern General Hospital & Glasgow Victoria Hospital), Davison S. (Leeds Children's Hospital), Dillon J. (Ninewells Hospital, Dundee), Forton D. (St George's Hospital, London), Foster G. (The London Hospital), Foxton M. (Chelsea & Westminster), Fraser A. (Aberdeen Royal Infirmary), Gelson W. (Addenbrookes Hospital, Cambridge), Gera A. (Queen Elizabeth Hospital, Woolwich), Geretti A. M. (Royal Liverpool University Hospital), Goldberg D. (Health Protection Scotland), Gorard D. (Wycombe Hospital), Gordon F. (Bristol Royal Infirmary), Gore C. (Hepatitis C Trust), Harris H. (Public Health England), Hayes P. (Royal Infirmary of Edinburgh), Heydtmann M. (Royal Alexandra Hospital, Glasgow), Higham A. (Royal Lancaster Infirmary), Holtham E. (University of Nottingham), Hubscher. (Queen Elizabeth Hospital, Birmingham), Hutchinson S. (Glasgow Caledonian University), Irving W. L. (University of Nottingham), Jenkins N. (Birmingham Heartlands Hospital), Kelly D. (Birmingham Children's Hospital), Kennedy N. (Monklands Hospital), Khakoo S. (Southampton General Hospital), Knowles J. (James Cook University Hospital, Middlesbrough), Langford A. (British Liver Trust), Lawson A. (Royal Derby Hospital), Leen C. (Western General Hospital, Edinburgh), Loganathan S. (Royal Aberdeen Childrens Hospital & Tayside Childrens Hospital, Dundee), McDonald S. E. (University of Glasgow), McLauchlan J. (University of Glasgow), McPherson S. (Freeman Hospital, Newcastle), Mills P. (Gartnavel General Hospital, Glasgow), Moreea S. (Bradford Teaching Hospitals NHS Foundation Trust), Mutimer D. (Queen Elizabeth Hospital, Birmingham), Nastouli E. (Great Ormond Street), Neal K. (Public Health England), Patel A. (University of Glasgow), Priest M. (Gartnavel General Hospital), Prince M. (Manchester Royal Infirmary), Quinlan P. (Advanced Data Analysis Centre, University of Nottingham), Reddy Y. (Royal Blackburn Hospital), Richardson P. (Royal Liverpool University Hospital), Rosenberg W. (Royal Free Hospital & University College Hospital), Ryder S. (Queen's Medical Centre, Nottingham), Shields P. (Royal Preston Hospital), Shorrock C. (Blackpool Victoria Hospital), Singhal S. (Sandwell & City Hospitals, Birmingham), Sreedharan A. (Lincoln County Hospital), Srirajaskanthan R. (University Hospital Lewisham), Stone B. (Royal Hallamshire Hospital, Sheffield), Thursz M. (St Mary's Hospital, London), Tudor-Williams G. (St Mary's Hospitals Paediatrics), Ustianowski A. (North Manchester General Hospital), Verma S. (Royal Sussex County Hospital, Brighton), Wilkes B. (University of Nottingham), Wiselka M. (Leicester Royal Infirmary). We acknowledge the tremendous support received from nurses and data entry clerks at all participating sites. We are also grateful to HCV Research UK, in particular Jennifer Benselin for collecting and collating data. Most of all, we acknowledge the participants themselves for agreeing to enrol in the cohort.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2018.11.013.

References

[1] Popping S, El-Sayed M, Feld J, et al. Report from the International Viral Hepatitis Elimination Meeting (IVHEM), 17–18 November 2017, Amsterdam, the Netherlands: gaps and challenges in the WHO 2030 hepatitis C elimination framework. J Virus Erad 2018;4:193–195.
[2] Pawlowska M, Sobolewska-Pilarczyk M, Domagalski K. Hepatitis C virus infection in children in the era of direct-acting antiviral. World J Gastroenterol 2018;24:2555–2566.
[3] WHO. Global hepatitis report, 2017. In: G. W. H. O. 2017., L. C. B.-N.-S. IGO. and C.-i.-P. (CIP) eds.; 2017:83.
[4] Ly KN, Hughes EM, Jiles RB, et al. Rising mortality associated with hepatitis C virus in the United States, 2003–2013. Clin Infect Dis 2016;62:1287–1288.
[5] Allison RD, Tong X, Moorman AC, et al. Increased incidence of cancer and cancer-related mortality among persons with chronic hepatitis C infection, 2006–2010. J Hepatol 2015;63:822–828.
[6] Cacoub P, Comarmond C, Domont F, et al. Extrahepatic manifestations of chronic hepatitis C virus infection. Ther Adv Infect Dis 2016;3:3–14.
[7] El-Shabrawi MH, Kamal NM. Burden of pediatric hepatitis C. World J Gastroenterol 2013;19:7880–7888.
[8] Rodrigue JR, Balistreri W, Haber B, et al. Impact of hepatitis C virus infection on children and their caregivers: quality of life, cognitive, and emotional outcomes. J Pediatr Gastroenterol Nutr 2009;48:341–347.
[9] Sokal E, Nannini P. Hepatitis C virus in children: the global picture. Arch Dis Child 2017;102:672–675.
[10] Shepard CW, Finelli L, Alter MJ. Global epidemiology of hepatitis C virus infection. Lancet Infect Dis 2005;5:558–567.
[11] Indolfi G, Hierro L, Dezsofi A, et al. Treatment of chronic hepatitis c virus infection in children: a position paper by the hepatology committee of European society of paediatric gastroenterology, hepatology and nutrition. J Pediatr Gastroenterol Nutr 2018;66:505–515.
[12] HCV Research UK. https://www.hcvresearchuk.org.
[13] McLauchlan J, Innes H, Dillon JF, et al. Cohort profile: the hepatitis C virus (HCV) research UK clinical database and biobank. Int J Epidemiol 2017.
[14] Ikeda K, Saitoh S, Suzuki Y, et al. Disease progression and hepatocellular carcinogenesis in patients with chronic viral hepatitis: a prospective observation of 2215 patients. J Hepatol 1998;28:930–938.
[15] Bortolotti F, Jara P, Diaz C, et al. Posttransfusion and community-acquired hepatitis C in childhood. J Pediatr Gastroenterol Nutr 1994;18:279–283.
[16] Locasciulli A, Testa M, Pontisso P, et al. Prevalence and natural history of hepatitis C infection in patients cured of childhood leukemia. Blood 1997;90:4628–4633.
[17] Bortolotti F, Verucchi G, Camma C, et al. Long-term course of chronic hepatitis C in children: from viral clearance to end-stage liver disease. Gastroenterology 2008;134:1900–1907.
[18] Mack CL, Gonzalez-Peralta RP, Gupta N, et al. NASPGHAN practice guidelines: diagnosis and management of hepatitis C infection in infants, children, and adolescents. J Pediatr Gastroenterol Nutr 2012;54:838–855.
[19] Robinson JL, Doucette K. The natural history of hepatitis C virus infection acquired during childhood. Liver Int 2012;32:258–270.
[20] Jara P, Resti M, Hierro L, et al. Chronic hepatitis C virus infection in childhood: clinical patterns and evolution in 224 white children. Clin Infect Dis 2003;36:275–280.
[21] Jara P, Hierro L. Treatment of hepatitis C in children. Expert Rev Gastroenterol Hepatol 2010;4:51–61.

[22] Mizuochi T, Takano T, Yanagi T, et al. Epidemiologic features of 348 children with hepatitis C virus infection over a 30-year period: a nationwide survey in Japan. J Gastroenterol 2018;53:419–426.
[23] Abdel-Hady M, Bunn SK, Sira J, et al. Chronic hepatitis C in children–review of natural history at a National Centre. J Viral Hepat 2011;18:e535–e540.
[24] Badizadegan K, Jonas MM, Ott MJ, et al. Histopathology of the liver in children with chronic hepatitis C viral infection. Hepatology 1998;28:1416–1423.
[25] Guido M, Bortolotti F, Leandro G, et al. Fibrosis in chronic hepatitis C acquired in infancy: is it only a matter of time? Am J Gastroenterol 2003;98:660–663.
[26] Camarero C, Ramos N, Moreno A, et al. Hepatitis C virus infection acquired in childhood. Eur J Pediatr 2008;167:219–224.
[27] Bortolotti F, Vajro P, Barbera C, et al. Hepatitis C in childhood: epidemiological and clinical aspects. Bone Marrow Transplant 1993;12 (Suppl 1):21–23.
[28] Garazzino S, Calitri C, Versace A, et al. Natural history of vertically acquired HCV infection and associated autoimmune phenomena. Eur J Pediatr 2014;173:1025–1031.
[29] Indolfi G, Bartolini E, Casavola D, et al. Chronic hepatitis C virus infection in children and adolescents: epidemiology, natural history, and assessment of the safety and efficacy of combination therapy. Adolesc Health Med Ther 2010;1:115–128.
[30] Khaderi S, Shepherd R, Goss JA, et al. Hepatitis C in the pediatric population: transmission, natural history, treatment and liver transplantation. World J Gastroenterol 2014;20:11281–11286.
[31] Indolfi G, Thorne C, El Sayed MH, et al. The challenge of treating children with hepatitis C virus infection. J Pediatr Gastroenterol Nutr 2017;64:851–854.
[32] Kanwal F, Kramer J, Asch SM, et al. Risk of hepatocellular cancer in HCV patients treated with direct-acting antiviral agents. Gastroenterology 2017;153, 996-1005.e1.
[33] Nagaoki Y, Aikata H, Nakano N, et al. 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;31:1009–1015.
[34] Westbrook RH, Dusheiko G. Natural history of hepatitis C. J Hepatol 2014;61(1 Suppl):S58–S68.
[35] Pawlowska M, Domagalski K, Pniewska A, et al. What's new in hepatitis C virus infections in children? World J Gastroenterol 2015;21:10783–10789.
[36] Tovo PA, Calitri C, Scolfaro C, et al. Vertically acquired hepatitis C virus infection: Correlates of transmission and disease progression. World J Gastroenterol 2016;22:1382–1392.
[37] El-Guindi MA, Hepatitis C. Viral infection in children: updated review. Pediatr Gastroenterol Hepatol Nutr 2016;19:83–95.
[38] Nwaohiri A, Schillie S, Bulterys M, et al. Towards elimination of hepatitis C virus infection in children. Lancet Child Adolescent Health 2018;2:235–237.
[39] Benova L, Mohamoud YA, Calvert C, et al. Vertical transmission of hepatitis C virus: systematic review and meta-analysis. Clin Infect Dis 2014;59:765–773.
[40] Gower E, Estes C, Blach S, et al. Global epidemiology and genotype distribution of the hepatitis C virus infection. J Hepatol 2014;61(1 Suppl):S45–S57.
[41] Larney S, Peacock A, Leung J, et al. Global, regional, and country-level coverage of interventions to prevent and manage HIV and hepatitis C among people who inject drugs: a systematic review. Lancet Glob Health 2017;5:e1208–e1220.
[42] Ainley LI, Hewitt PE. Haematology patients and the risk of transfusion transmitted infection. Br J Haematol 2018;180:473–483.
[43] Bruno S, Di Marco V, Iavarone M, et al. Survival of patients with HCV cirrhosis and sustained virologic response is similar to the general population. J Hepatol 2016;64:1217–1223.
[44] Negro F, Forton D, Craxi A, et al. Extrahepatic morbidity and mortality of chronic hepatitis C. Gastroenterology 2015;149:1345–1360.
[45] El-Serag HB, Kanwal F, Richardson P, et al. Risk of hepatocellular carcinoma after sustained virological response in Veterans with hepatitis C virus infection. Hepatology 2016;64:130–137.
[46] Sutton AJ, Gay NJ, Edmunds WJ, et al. Modelling the force of infection for hepatitis B and hepatitis C in injecting drug users in England and Wales. BMC Infect Dis 2006;6:93.
[47] Mohan P, Colvin C, Glymph C, et al. Clinical spectrum and histopathologic features of chronic hepatitis C infection in children. J Pediatr 2007;150:168–174, 74.e1.