Chapter 11
Viral Hepatitis: Hepatitis C

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Questions

What Are the Risk Factors for HCV Infection and What Are the Clinical Features of Acute Hepatitis C?

Acute hepatitis C (AHC) has a spectrum of clinical presentation and course, and its diagnosis can be challenging in a significant proportion of patients. Risk factors of HCV infection and persons for whom HCV screening is recommended are summarized in Table 11.1 [1]. However, it should be noted that these risk factors may not be present in up to one-third of patients, especially among Asians [2–4]. The prompt diagnosis of AHC is crucial in order to allow close monitoring and early treatment, which effectively prevent disease transmission and consequences of liver disease. Nowadays, AHC is often encountered among intravenous drug users, men who have sex with men, and in the health care-associated settings [3–5].

Clinical presentation of AHC ranges from asymptomatic alanine aminotransferase (ALT) elevation to acute icteric hepatitis with symptoms of nausea, vomiting, and abdominal pain [3–5]. The most frequently used individual criteria for defining

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Table 11.1 Risk factors for HCV infection and the recommendation for HCV testing

Persons born between 1945 and 1965
Persons with risk behaviors, exposures, and conditions associated with an increased risk of HCV infection
• Risk behaviors
– Injection-drug use (current or ever)
– Intranasal illicit drug use
• Risk exposures
– Long-term dialysis
– Getting a tattoo or body piercing in unregulated setting
– Healthcare, emergency medical and public safety workers after needle sticks, sharps, or mucosal exposure to HCV-related blood
– Children born to HCV-infected women
– Prior recipients of transfusions or organ transplantation before 1992
– Persons who were ever incarcerated
• Other medical conditions
– HIV infection
– Unexplained chronic liver disease and chronic hepatitis
– Medical conditions that may causality related to HCV infection, such as mixed cryoglobulinemia and membranoproliferative glomerulonephritis

a case includes anti-HCV seroconversion, acute ALT elevation, and HCV-RNA detection [6]. Testing for anti-HCV alone cannot be used to diagnose AHC in the early phase, since it generally is detected after 4–12 weeks after HCV inoculation [3–5]. Substantial changes in HCV-RNA and ALT activity are commonly seen in patients with AHC, whereas intermittent and transient HCV-RNA negativity and ALT normalization can also be observed [4, 5, 7]. Thus, patients with acute hepatitis C warrant careful monitoring with repeated testing of HCV-RNA, ALT and serology, as well as exclusion of other causes of acute hepatitis.

The majority (60–80 %) of individuals exposed to HCV evolve on to chronic infection [3]. Several host and viral factors, including younger age, female gender, presence of symptoms and/or jaundice, antiviral broadly specific, durable and polyfunctional T cell response, immunogenetic polymorphisms such as IL28B, human immune-deficiency virus (HIV) infection, low dose HCV inoculum, and high initial HCV-RNA, have been known to favorably impact spontaneous resolution of acute hepatitis C [3–5, 8, 9]. Approximately 80 % of patients with self-limiting hepatitis C experience HCV-RNA clearance within 3 months of onset of infection. Persistent viremia beyond 6 months of infection is usually associated with evolution to chronic infection [10–12].

The *European Association for the Study of the Liver* (EASL) guidelines suggest following HCV-RNA every 4 weeks, and that only those who remain positive at 12 weeks from onset be treated [13–15]. Treatment of AHC had traditionally been with pegylated interferon (PEG-IFN) monotherapy for 12–24 weeks, with expected successful rate around 90 % [12–17]. Initiation of treatment before or at week 12 after onset of AHC results in higher sustained virological response (SVR) rates than

initiation beyond week 20 [15, 18]. The combination of PEG-IFN plus ribavirin (RBV) and direct acting antivirals (DAA)-based regimens are also likely to be effective in AHC, but these need large clinical trials to confirm [1, 14]. Also, the use of DAAs alone is likely to be influenced by their availability in resource constrained regions of the World.

What Are the Natural History and the Consequences of Chronic HCV Infection?

Persistent viremia beyond 6 months of infection indicates chronic infection [10–12]. Once chronic infection is established, spontaneous clearance of HCV is very rare. Published estimates of fibrosis progression and time to cirrhosis are dependent on study design and the patient population, while one large systematic review of 111 studies estimated prevalence of cirrhosis at 20 years after the infection to be 14–19 % [19] (Fig. 11.1). Fibrosis progression in chronic hepatitis C is variable and depends on numerous host, viral, and environmental factors, such as age at acquisition of infection, sex, race, genetic factors, alcohol consumption, insulin resistance, and coinfection with other viruses [20] (Table 11.2). Identification of these factors is important because modifiable factors can be altered and high-risk patients should be treated promptly. For example, insulin resistance, obesity, and/or hepatic steatosis

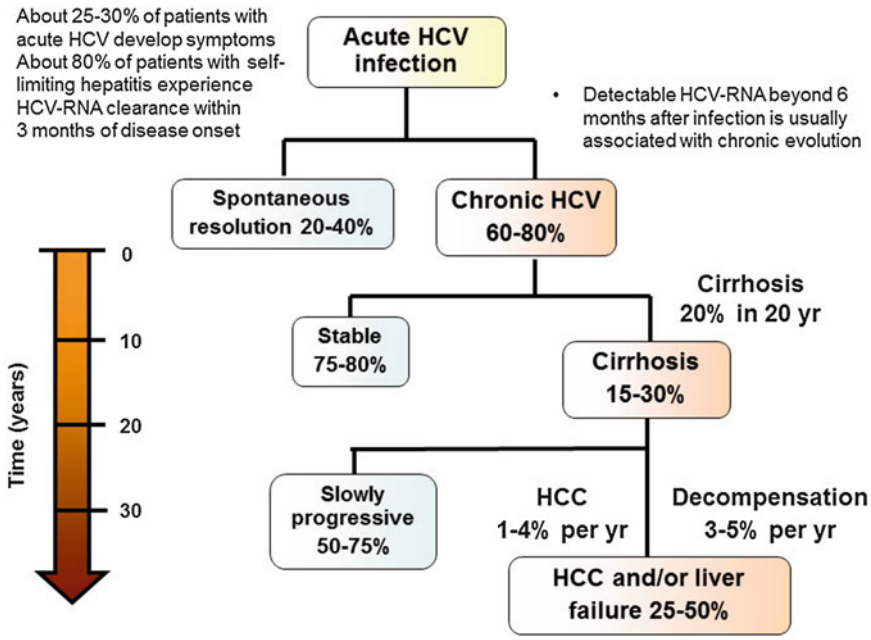

Fig. 11.1 Natural history of hepatitis C. *HCV* hepatitis C virus, *HCC* hepatocellular carcinoma

Table 11.2 Factors associated with HCV disease progression

Established factors	Possible factors
• Age at infection >40 years	• Male gender
• Caucasians	• HCV genotype 3
• Obesity[a]	• Cigarette smoking[a]
• Fatty liver[a]	• Increased hepatic iron concentration
• Metabolic syndrome/insulin resistance[a]	• High level of serum transaminases
• Alcohol consumption >20 g/day[a]	
• Daily use of marijuana[a]	
• Immunosuppressed state[a]	
• Schistosomiasis	
• HIV coinfection	
• Hepatitis B coinfection	

[a]Modifiable risk factors

have shown to accelerate progression of fibrosis and possibly increase risk of HCC in patients with HCV [21]. Weight reduction is associated with decrease in hepatic steatosis and the rate of fibrosis progression [21].

It should be noted that serum ALT level has high visit-to-visit variability and is not a good indicator of liver disease activity or fibrosis in HCV patients [22]. Prospective data from community-based cohort of 1,235 HCV-infected persons found that ALT levels were persistently normal in 42 %, persistently elevated in 15 %, and intermittently elevated in 43 % [22]. Patients with persistently normal serum ALT levels tend to have significantly lower scores for inflammation and fibrosis, compared with patients with elevated serum ALT levels; however advanced fibrosis/cirrhosis and portal inflammation can be observed histologically in 12 and 26 % of those with persistently normal and abnormal ALT, respectively [23]. Traditionally, the gold standard for the assessment of the stage of fibrosis in HCV has been to perform percutaneous liver biopsy and then staging by METAVIR, Ishak, or Knodell scoring systems. However, in real-life practice, liver biopsy may be limited by patient's acceptance, pain, risk of bleeding, and the possibility for sampling error. Therefore, noninvasive methods to assess liver injury and fibrosis (e.g., transient elastography, serum direct and indirect fibrotic markers) have been evaluated and are becoming increasingly available and used. Although no single noninvasive test or combination of tests developed to date can parallel the information obtained from actual histology, noninvasive methods, particularly when used in combination, can reliably differentiate between minimal and significant fibrosis or cirrhosis, and thereby avoid liver biopsy in a significant percentage of patients [24].

Among patients with HCV-induced cirrhosis, manifestations of liver failure (e.g., ascites, variceal bleeding, encephalopathy, and hepatorenal syndrome) develop in 3–5 % per year, and HCC develops in 1–4 % per year [25–27]. Once decompensation has developed, survival rate is about 50 % at 5 years and LT is the only effective therapy [25–27] (Fig. 11.1).

HCV infection can be associated with other extrahepatic conditions, such as impaired quality of life, insulin resistance, mental impairment, depression, lymphoproliferative

(e.g., essential mixed cryoglobulinemia and lymphoma) and autoimmune disorders [28, 29]. Further, HCV generates a major financial burden to society. In 1997, the total cost of HCV-related illness in the USA was estimated to be $5.46 billion ($1.80 billion direct costs and $3.66 billion indirect costs) [30]. The projected annual direct medical care cost of HCV treatment from 2010 to 2019 is $6.5–$13.6 billion, with indirect costs expected to reach $75.5 billion [31].

Do I Require Treatment for Chronic Hepatitis C?

Antiviral therapy should be considered for all patients with chronic HCV infection. In most circumstances, the decision of whether or not to proceed with treatment is based on the patient's desire and the need for therapy. The degree of the need is a subjective assessment that is made upon considering the stage of liver disease, presence or absence of favorable factors for treatment response, safety and efficacy of the available treatment options, age and comorbid conditions.

The primary goal of treatment of HCV infection is eradication or "cure" of the virus. Sustained virologic response (SVR, undetectable HCV-RNA by sensitive assay after 12–24 weeks after completion of therapy) is known to be an excellent surrogate marker for the cure of HCV. In an extensive review of 44 long-term follow studies after treatment-induced SVR, HCV-RNA was noted to have remained undetectable in 97 % of a combined total of >4,000 HCV patients, many of whom were immunosuppressed, during their follow-up periods (range from 2 to >10 years) [32, 33]. Several studies have clearly demonstrated that SVR is associated with a substantial reduction in hepatic inflammation, reversal of fibrosis and even of cirrhosis, as well as improvement in health-related quality of life [34–38]. Hence, the risk of liver failure, at least over the short term, is virtually eliminated in patients with cirrhosis who achieve an SVR [36–38]. Notably, the risk of HCC after SVR in patients with cirrhosis is reduced by more than one half; however the risk is not eliminated and surveillance for HCC in cirrhotics must continue [37, 38]. Additional cirrhosis care, in those who achieved SVR, such as surveillance for varices is necessary although we currently do not know if the frequency of surveillance should remain the same as for those without viral clearance or those with other etiologies for cirrhosis. Successful treatment of HCV has been associated with a decrease in liver related mortality, need for liver transplantation, and also with a decrease in all-cause mortality [39].

How Effective Has Interferon-Based Regimen Been and What Have the Challenges Been?

Interferon-based regimen, mainly with PEG-IFN plus ribavirin (RBV), had been the standard of care of HCV therapy for more than a decade [14, 40]. Two forms of PEG-IFN are available (PEG-IFN alfa-2a and alfa-2b), and RBV should be

administered according to the body weight of the patient. Although smaller trials from Europe have suggested slightly higher SVR rates with PEG-IFN alfa-2a [41, 42], a large US multicenter study did not detect any significant difference in SVR between the two PEG-IFNs plus RBV [43]. While IFN-based therapies have almost been completely replaced by IFN-free DAA-based therapies in the USA, a combination of PEG-IFN/RBV will be still widely utilized in the developing countries for quite some time because access to new drugs are restricted and delayed by policies, limited resources, and economic barriers.

PEG-IFN/RBV treatment is administered for either 48 weeks (for HCV genotypes 1, 4, 5, and 6) or for 24 weeks (for HCV genotypes 2 and 3), inducing SVR rates of 40–50 % in those with genotype 1, 50–60 % in those with genotype 4, 60–90 % in those with genotype 6, and >70–85 % in those with genotypes 2 and 3 infection [14, 40, 44]. Several host (e.g., age, race, IL-28 B genotype, obesity, metabolic, comorbidities and presence of advanced fibrosis and cirrhosis), viral (e.g., viral load and genotype), environmental (e.g., substance and alcohol abuse), and treatment-related factors (e.g., side effects, adherent to therapy) have been shown to influence the SVR rates following IFN-based therapy. It should be noted that HCV treatment outcome with PEG-IFN/RBV in Asians seems to be superior to that of non-Asian populations, and this may be due to several factors that include a favorable IL28B genotype [2, 44]. Host genetic polymorphisms located on chromosome 19 near the region coding for IL28B (or IFN lambda-3) is associated with SVR following treatment with PEG-IFN/RBV in HCV genotype 1, but also to a lesser extent for genotype 2 and 3 [45, 46]. IL28B testing is useful to predict virologic response at week 4 as a predictive marker for the success of treatment with PEG-IFN/RBV, but its role in protease inhibitor-based triple therapy is less significant, and is insignificant in IFN-free treatment regimen [45, 46]. Improvement of SVR rates with IFN-based therapy can be achievable by correction of modifiable risk factors, treatment adherence and response-guided adjustment of the treatment duration (response-guided therapy, RGT) [14] (Fig. 11.2).

One of the challenges in utilizing PEG-IFN/RBV therapy is management of the treatment-related side effects. The common side effects of PEG-IFN include influenza-like syndrome (fever, headache, malaise, and myalgia), cytopenia, sleep disturbance, hair loss and psychiatric effects, whereas the unusual and severe side effects include seizure, psychosis, severe depression, autoimmune reactions, bacterial infections, and thyroid dysfunction. The major side effects of RBV are hemolytic anemia, cough, rash, and teratogenicity. These side effects are generally manageable by pretreatment advice, proper clinical and laboratory monitoring, symptomatic treatment, and appropriate dose reduction of the related drugs. In cases with significant RBV-induced anemia (hemoglobin <10 g/dL), a stepwise RBV dose decrement is suggested to maintain RBV exposure during treatment in order to minimize virologic relapse [14, 47]. This strategy has been proven not to compromise the SVR rate, and erythropoiesis-stimulating agents may also be useful in select patients with difficulty in management of anemia especially in those with cirrhosis and/or multiple comorbidities [47, 48].

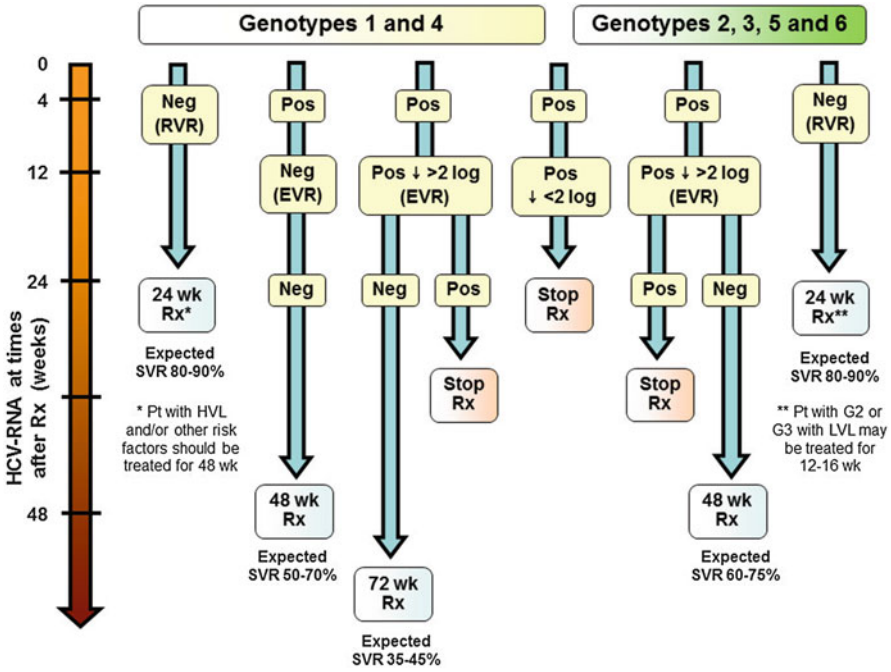

Fig. 11.2 Recommendations for response-guided therapy with pegylated interferon plus ribavirin and the expected sustained virological response rates. *SVR* sustained virological response, *RVR* rapid virological response, *EVR* early virological response, *HVL* high viral load, *LVL* low viral load, *Pt* patients, *G* genotype

What Are the Current Treatment Options?

Therapies for chronic HCV have been evolving rapidly over the past few years, mainly due the development of new DAA targeting NS3/4A, NS5A, and NS5B HCV proteins (Table 11.3) [1, 13, 49, 50]. Accordingly, treatment-induced SVR rates have been consistently improving, and now IFN-free DAA combination regimen with short duration of treatment (<3 months), single or few pills per day, and >95 % SVR rates have become widely available. Currently, some of these all-oral combinations (such as sofosbuvir/ledipasvir with or without RBV, sofosbuvir plus simeprevir, paritaprevir/ritonavir/ombitasvir plus dasabuvir with or without RBV) have already been approved in the USA and some countries in Europe. Most recently, daclatasvir in combination with sofosbuvir with or without RBV has also been approved for use in the USA, and previously in Europe and in Japan and provides a viable option particularly for those with genotype 3 infection. At this evolving stage of HCV management, it is suggested to continuously update the most recent recommendations for HCV treatment via the American Association for the Study of Liver Disease (AASLD), and EASL websites [1, 13]. The recent Infectious

Table 11.3 Pharmacologic properties and potential for drug–drug interactions of anti-HCV medications

Drugs	Metabolism/excretion route	Interaction with CYP and substrate transporters	Dosage adjustment in patients with renal impairment (RI)	Dosage adjustment in patients with liver impairment
Pegylated interferons (PEG-IFN)				
PEG-IFN alfa-2a	Renal (main) and hepatic (minor)	No	135 μg/week (25–45 % reduction) for severe RI/ESRD	Not recommended for CTP class B/C
PEG-IFN alfa-2b	Renal	No	1.125 μg/kg/week (25 % reduction) for moderate RI; 0.75 μg/kg/week (50 % reduction) for severe RI/ESRD	Not recommended for CTP class B/C
Ribavirin				
Ribavirin	Renal	No	200–400 mg/day for moderate RI; 200 mg/day for severe RI/ESRD	No dose adjustment is required for cirrhosis (with careful monitoring)
NS3/4A protease inhibitors				
Telaprevir	Hepatic (CYP3A)	Strong CYP3A inhibitor, moderate P-gp inhibitor	No dose adjustment is required for any degree of RI (clinical data is limited)	No dose adjustment is required in compensated cirrhosis; not recommended for CTP class B/C
Boceprevir	Hepatic (CYP3A, aldoketo-reductase)	Moderate CYP3A inhibitor, weak P-gp inhibitor	No dose adjustment is required for any degree of RI (clinical data is limited)	No dose adjustment is required in compensated cirrhosis; not recommended for CTP class B/C
Simeprevir	Hepatic (CYP3A)	Mild CYP1A2 and CYP3A inhibitor, inhibitor of OATP1B1 and MRP2	No dose adjustment is required for mild-severe RI; no data in ESRD	No dose adjustment is required in compensated cirrhosis; not recommended for CTP class C
Paritaprevir (ABT-450)/ritonavir	Hepatic (CYP3A)	Strong CYP3A inhibitor (ritonavir), inhibitor of OATP1B1, substrate of P-gp and BCRP	No dose adjustment is required for mild-moderate RI; no data in severe RI/ESRD	No dose adjustment is required in compensated cirrhosis; not recommended for CTP class C

Asunaprevir	Hepatic (CYP3A)	Weak CYP3A4 inducer, moderate CYP2D6 inhibitor, inhibitor of P-gp and OATP1B1	No dose adjustment is required for any degree of RI (clinical data is limited)	No dose adjustment is required in compensated cirrhosis; not recommended for CTP class B/C
NS5A replication complex inhibitors				
Daclatasvir	Hepatic (CYP3A)	Not a CYP3A inducer/inhibitor, moderate inhibitor of P-gp and OATP1B1	No dose adjustment is required for any degree of RI (clinical data is limited)	No dose adjustment is required in compensated cirrhosis; not recommended for CTP class C
Ledipasvir	Feces (major); hepatic and renal (minor)	Not a CYP inducer/inhibitor, weak inhibitor of P-gp and OATP1B1	No dose adjustment is required for mild-moderate RI; no data in severe RI/ESRD	No dose adjustment is required for any degree of liver impairment
Ombitasvir (ABT-267)	Amide hydrolysis and oxidative metabolism	Not a CYP inducer/inhibitor, substrate of P-gp and BCRP	No dose adjustment is required for mild-moderate RI; no data in severe RI/ESRD	No dose adjustment is required in compensated cirrhosis; not recommended for CTP class C
NS5B nucleotide polymerase inhibitors				
Sofosbuvir	Renal	Not a CYP inducer/inhibitor, substrate of P-gp	No dose adjustment is required for mild-moderate RI; no data in severe RI/ESRD	No dose adjustment is required for any degree of liver impairment
NS5B non-nucleoside polymerase inhibitors				
Dasabuvir (ABT-333)	Hepatic (CYP2C8 60 %, CYP3A4 30 % and CYP2D6 10 %)	Not a CYP inducer/inhibitor, substrate of P-gp and BCRP	No dose adjustment is required for mild-moderate RI; no data in severe RI/ESRD	No dose adjustment is required in compensated cirrhosis; not recommended for CTP class C

Adapted from Tischer S, Fontana RJ. J Hepatol 2014;60:872–84 and Bunchorntavakul C, Tanwandee T. Gastroenterol Clin North Am 2015; in press
CYP cytochrome P450, *P-gp* P-glycoprotein, *BCRP* breast cancer resistance protein, *MRP* multiple drug resistance protein, *OATP* organic anion transporting polypeptide, *RI* renal impairment, *ESRD* end-stage renal disease, *CTP* Child–Turcotte–Pugh

Diseases Society of America (IDSA)/AASLD guidance is summarized in Table 11.4, and with these regimens, the expected SVR rates are over 90 % for non-cirrhotic and cirrhotic patients with any of the HCV genotypes [1]. However, in real-life practice, treatment regimen for HCV may not be generalizable due to many reasons such as patient's comorbidities, physician's preference, availability and cost of DAA in each country, as well as the reimbursement policy. Therefore, the appropriate HCV treatment regimens should be tailored based on the risk of progressive liver disease in an individual patient, associated comorbidities, local or regional treatment guidelines and cost-effectiveness analyses.

What Are the Challenges, If Any, in Treating Special Populations Such as Those With, Renal Failure, Decompensated Liver Disease, Liver Transplantation, and HIV Infection?

The management of HCV in special populations is challenging, particularly when treating with IFN-based therapy, due to reduced efficacy of treatment, increased treatment-related side effects, altered pharmacokinetics, as well as the potential for drug–drug interactions. Important pharmacokinetic and metabolic properties of PEG-IFN, RBV and selected DAA are summarized in Table 11.3 [49, 50]. New generation DAA-based therapy, especially the IFN-free/RBV-free regimens, are preferred. The efficacy and safety data of the currently approved all-oral DAA combinations is compelling for use is special HCV populations, as recently been recommended by the AASLD/IDSA guidance (Table 11.5).

HCV Infection in Patients with End-Stage Renal Disease (ESRD) (Fig. 11.3)

HCV infection in patients with ESRD is associated with more rapid liver disease progression, more liver-related mortality and reduced renal graft and patient survival following kidney transplantation [51–55]. It should also be noted that serum ALT levels in patients with ESRD are lower than in the general population, and there is a weak correlation between ALT levels and liver disease activity in this population [53, 56]. The pharmacokinetics of IFN, RBV and some DAA, such as sofosbuvir, are altered in patients with ESRD. With dose adjustment and careful monitoring, treatment with PEG-IFN plus RBV in HCV patients with ESRD can be associated with SVR rates nearly comparable to those with normal renal function [53, 56, 57]. In patients with severe renal impairment (creatinine clearance, CrCl <30 mL/min) or ESRD on dialysis, the dose recommendations are 135 μg/week for PEG-IFN alfa-2A, and 1 μg/kg/week or 50 % reduction for PEG-IFN alfa-2B), and 200 mg/day for ribavirin [1]. Based on the

Table 11.4 AASLD/IDSA guidance for the treatment of chronic HCV infection

	Treatment-naïve patients	Patients whom prior PEG-IFN plus RBV treatment has failed
HCV genotype 1a	• SOF-LDV for 12 weeks • PTV-RTV-OMV + DSV + RBV for 12 weeks (no cirrhosis) or 24 weeks (cirrhosis) • SOF + SMV, ±RBV for 12 weeks (no cirrhosis) or 24 weeks (cirrhosis) • DCV + SOF for 12 weeks (no cirrhosis) or DCV + SOF ± RBV for 24 weeks (cirrhosis)	• Same as treatment-naïve • Patients in whom PEG-IFN + RBV ± PI has failed: SOF-LDV for 12 weeks (no cirrhosis) or SOF-LDV + RBV for 12 weeks (cirrhosis) or SOF-LDV 24 week (cirrhosis)
HCV genotype 1b	• SOF-LDV for 12 weeks • PTV-RTV-OMV + DSV for 12 weeks • SOF + SMV ± RBV for 12 weeks (no cirrhosis) or 24 weeks (cirrhosis) • DCV + SOF for 12 weeks (no cirrhosis) or DCV + SOF ± RBV for 24 weeks (cirrhosis)	• Same as treatment-naïve • Patients in whom PEG-IFN + RBV ± PI has failed: SOF-LDV for 12 weeks (no cirrhosis) or SOF-LDV + RBV for 12 weeks (cirrhosis) or SOF-LDV 24 week (cirrhosis)
HCV genotype 2	• SOF + RBV for 12 weeks (no cirrhosis) or 16 weeks (cirrhosis) • DCV + SOF for 12 weeks (no cirrhosis) or for 16 weeks (cirrhosis) in RBV-intolerant	• SOF + RBV for 16–24 weeks • SOF + RBV + PEG-IFN[a] for 12 weeks • DCV + SOF ± RBV[a] for 24 weeks if IFN-ineligible
HCV genotype 3	• DCV + SOF for 12 weeks (no cirrhosis) or DCV + SOF ± RBV for 24 weeks (cirrhosis) • SOF + RBV + PEG-IFN for 12 weeks if IFN-eligible • SOF + RBV[a] for 24 weeks	• Same as treatment naïve
HCV genotype 4	• SOF-LDV for 12 weeks • PTV-RTV-OMV + DSV + RBV for 12 weeks • SOF + RBV for 24 weeks • SOF + RBV + PEG-IFN[a] for 12 weeks	• Same as treatment-naïve • SOF + RBV + PEG-IFN for 12 weeks
HCV genotype 5	• SOF-LDV for 12 weeks • SOF + RBV + PEG-IFN[a] for 12 weeks	• Same as treatment-naïve
HCV genotype 6	• SOF-LDV for 12 weeks • SOF + RBV + PEG-IFN[a] for 12 weeks	• Same as treatment-naïve

SOF sofosbuvir, *LDV* ledipasvir, *SMV* simeprevir, *PTV* paritaprevir, *RTV* ritonavir, *OMV* ombitasvir, *DSV* dasabuvir, *PEG-IFN* pegylated interferon, *RBV* ribavirin, *DCV* daclatasvir, *PI* protease inhibitors
[a]Alternative regimens

Table 11.5 Summary of AASLD/IDSA guidance for the treatment of chronic HCV infection in special populations

Decompensated cirrhosis	
HCV genotype 1 or 4	• SOF-LDV + RBV (initial dose of 600 mg, increased as tolerate) for 12 weeks (consider 24 weeks for prior sofosbuvir failure) • DCV + SOF + RBV (initial dose of 600 mg, increased as tolerate) for 12 weeks • DCV + SOF for 24 weeks (if RBV intolerant or ineligible)
HCV genotype 2 or 3	• DCV + SOF + RBV (initial dose of 600 mg, increased as tolerate) for 12 weeks • SOF + RBV for up to 48 weeks
Recurrent HCV post liver transplantation	
HCV genotype 1	• SOF-LDV + RBV for 12 weeks (including compensated cirrhosis) • DCV + SOF + RBV (initial dose of 600 mg, increased as tolerate) for 12 weeks (including compensated cirrhosis) • SOF-LDV[a] for 24 weeks (including compensated cirrhosis) • DCV + SOF[a] for 24 weeks (including compensated cirrhosis) • PTV-RTV-OMV + DSV + RBV[a] for 24 weeks (for early recurrence: fibrosis stage 0–2) • SOF[a] + SMV ± RBV for 12 weeks
HCV genotype 2	• DCV + SOF + RBV (initial dose of 600 mg, increased as tolerate) for 12 weeks • SOF + RBV for 24 weeks • DCV[a] + SOF for 24 weeks
HCV genotype 3	• DCV + SOF + RBV (initial dose of 600 mg, increased as tolerate) for 12 weeks • SOF + RBV for 24 weeks • DCV[a] + SOF for 24 weeks
HCV genotype 4	• SOF-LDV + RBV for 12 weeks • DCV + SOF + RBV (initial dose of 600 mg, increased as tolerate) for 12 weeks • SOF-LDV[a] for 24 weeks • DCV[a] + SOF for 24 weeks
HIV-HCV coinfection	
DCV	• DCV requires dose adjustment with ritonavir-boosted atazanavir (a decrease to 30 mg daily) and efavirenz or etravirine (an increase to 90 mg daily)
SOF-LDV	• Because LDV increases tenofovir levels, concomitant use of LDV with tenofovir disoproxil fumarate mandates consideration of CrCl rate and should be avoided in those with CrCl below 60 mL/min • Because potentiation of this effect is expected when tenofovir is used with RTV-boosted HIV protease inhibitors, LDV should be avoided with this combination (pending further data) unless ARV cannot be changed and the urgency of treatment is high

(continued)

Table 11.5 (continued)

PTV-RTV-OMV + DSV	• PTV-RTV-OMV + DSV should be used with ARV with which it does not have substantial interactions: raltegravir, dolutegravir, enfuvirtide, tenofovir, emtricitabine, lamivudine, and atazanavir • The dose of RTV used for boosting of HIV protease inhibitors may need to be adjusted (or held) when administered with PTV-RTV-OMV + DSV and then restored when HCV treatment is completed • HIV protease inhibitor should be administered at the same time as the fixed-dose HCV combination
SMV	• SMV should only be used with ARV with which it does not have clinically significant interactions: raltegravir (and probably dolutegravir), rilpivirine, maraviroc, enfuvirtide, tenofovir, emtricitabine, lamivudine, and abacavir

SOF sofosbuvir, *LDV* ledipasvir, *SMV* simeprevir, *PTV* paritaprevir, *RTV* ritonavir, *OMV* ombitasvir, *DSV* dasabuvir, *PEG-IFN* pegylated interferon, *RBV* ribavirin, *DCV* daclatasvir, *PI* protease inhibitors

[a]Alternative regimens

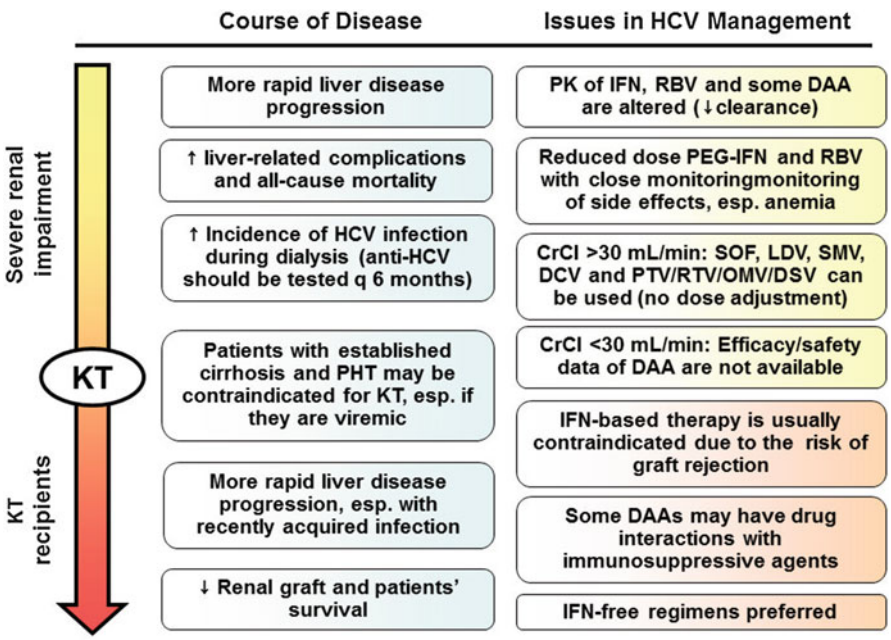

Fig. 11.3 Natural history and management of hepatitis C in patients with severe renal impairment and kidney transplantation. *HCV* hepatitis C virus, *KT* kidney transplantation, *PHT* portal hypertension, *PEG-IFN* pegylated interferon, *RBV* ribavirin, *PK* pharmacokinetics, *DAA* direct acting antivirals, *SOF* sofosbuvir, *LDV* ledipasvir, *DCV* daclatasvir, *SMV* simeprevir, *PTV* paritaprevir, *RTV* ritonavir, *OMV* ombitasvir, *DSV* dasabuvir, *CrCl* creatinine clearance

available data, the AASLD/IDSA guidance advised that no dose reduction is needed when using sofosbuvir in HCV patients with mild to moderate renal impairment (CrCl ≥30 mL/min). However, sofosbuvir is not recommended in patients with severe renal impairment/ESRD (CrCl <30 mL/min) or those who require dialysis until more data becomes available [1]. For DAA with primarily hepatic metabolism (e.g., boceprevir, simeprevir, daclatasvir), no dosage adjustment is required for patients with mild/moderate to severe renal impairment although these agents have not been adequately studied in patients with ESRD, including those requiring dialysis [1]. For patients with mild to moderate renal impairment (CrCl >30 mL/min), no dose adjustment is required when using sofosbuvir, simeprevir, fixed-dose combination of sofosbuvir/ledipasvir, or fixed-dose combination of paritaprevir/ritonavir/ombitasvir plus dasabuvir [1]. However, the safety and efficacy data of all-oral DAA regimens are limited in those with CrCl <30 mL/min [1].

HCV Infection in Patients with Decompensated Cirrhosis (Fig. 11.4)

Treatment of HCV is strongly recommended for patients with advanced fibrosis and compensated cirrhosis as an SVR in this high-risk group is associated with a significant decrease of the incidence of clinical decompensation and HCC [38, 39]. Further, successful viral eradication may then facilitate delay, or, in a small proportion of patients, avoid liver transplantation, as well as prevent HCV recurrence following liver transplantation. However, the SVR rates are generally lower with IFN-based therapies and side effects occur more commonly in patients with advanced fibrosis or cirrhosis when compared to patients with mild to moderate fibrosis [38, 39, 58]. Treatment with PEG-IFN/RBV in patients with decompensated cirrhosis is somewhat disappointing due to low efficacy (SVR 7–30 % for genotype 1, and 44–57 % for genotype 2/3) and high rates of treatment-related side effects (led to dose reduction in 40–70 % and treatment discontinuation in 13–40 %) [59, 60]. A French cohort (CUPIC Study Group) of HCV cirrhosis treated with boceprevir- or telaprevir-based triple therapy ($N=674$) reported a high incidence of serious adverse events, including death, in those with platelet count <100,000/mm^3 and/or albumin <3.5 g/L at baseline [61]. Further the real-world experience (HCV-TARGET study ($N=2084$; 38 % had cirrhosis) revealed that triple therapy was associated with high rate of adverse events (12 % had serious adverse events) and involved frequent treatment modifications [62]. Therefore, these triple therapies have no role in patients with decompensated liver disease, and newer generation DAA, preferably IFN-free regimens, are required in this population. The pharmacokinetics of sofosbuvir, ledipasvir and daclatasvir do not appear to change significantly in patients with moderate or severe liver impairment. A fixed-dose combination of paritaprevir/ritonavir/ombitasvir plus dasabuvir and RBV appear to be safe in patients with compensated cirrhosis, but should not be used in decompensated patients. Similarly, simpeprevir is not recommended in Child Class B and C cirrhosis. The AASLD/IDSA guideline recommends that patients with decompensated cirrhosis can be treated with all-oral DAA

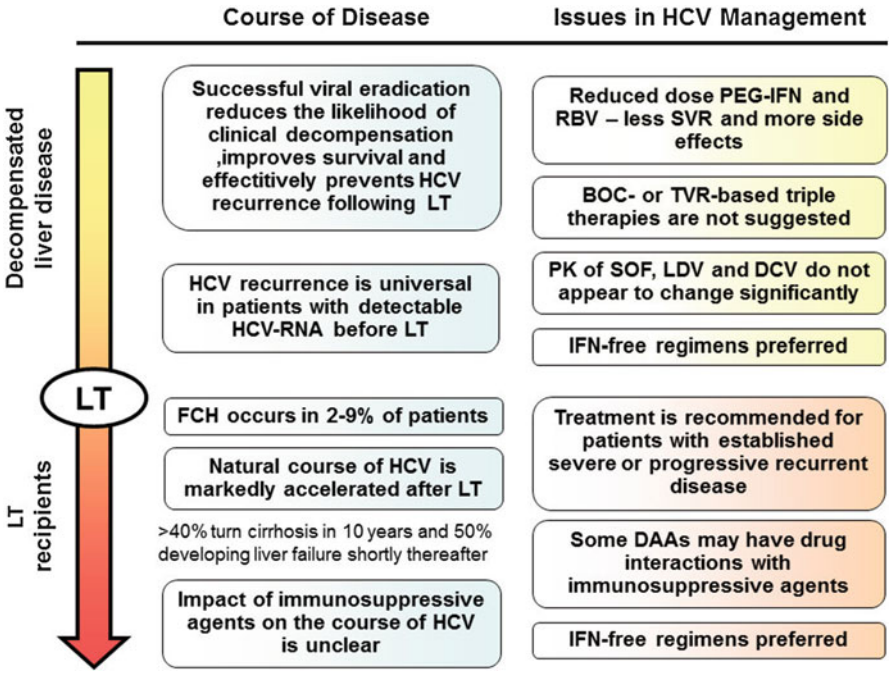

Fig. 11.4 Natural history and management of hepatitis C in patients with decompensated liver disease and liver transplantation. *HCV* hepatitis C virus, *LT* liver transplantation, *FCH* fibrosing cholestatic hepatitis, *SVR* sustained virological response, *PEG-IFN* pegylated interferon, *RBV* ribavirin, *DAA* direct acting antivirals, *PK* pharmacokinetics, *BOC* boceprevir, *TVR* telaprevir, *SOF* sofosbuvir, *LDV* ledipasvir, *DCV* daclatasvir

regimens containing sofosbuvir, ledipasvir, and RBV, according to the HCV genotypes (Table 11.5). These recommended all-oral combination regimens are generally associated with SVR rates nearly similar to that of patients without decompensated cirrhosis [1]. The majority of patients with decompensated cirrhosis will improve their liver function following SVR, which may sometimes facilitate the avoidance of liver transplantation; however liver disease progression can be observed in some patients, particularly those with pretreatment MELD >15 [63]. The antiviral treatment should be started at least 3 months before anticipated surgery with a goal of undetectable HCV-RNA for at least 30 days [63].

HCV Infection in Liver Transplant Recipients (Fig. 11.4)

Liver transplantation in HCV patients is associated with suboptimal graft survival which is attributable to universal recurrence of HCV in the graft [59, 64, 65]. The natural course of HCV is accelerated in liver transplant recipients, with more than

40 % progressing to cirrhosis within 10 years and approximately 50 % developing liver failure shortly thereafter [59, 64, 65]. The recommended standard of care for liver transplant recipients is treatment of confirmed significant or progressive recurrent HCV disease, based either on persistent, unexplained elevated ALT levels or on histologically confirmed fibrosis once rejection, biliary obstruction, vascular complication, and other causes have been excluded [59, 64, 65]. Due to the lack of sensitivity and specificity of serum ALT in determining the severity of recurrent hepatitis C, HCV recipients ideally should undergo protocol liver biopsies starting from around 6–12 months following liver transplantation [59, 64, 65]. The availability and high success rate of DAAs in treating this patient population may ultimately obviate the need for protocol biopsies. Treatment with PEG-IFN/RBV is associated with SVR rates of 24–40 % in LT recipients, but adverse effects are common (two-thirds of patients required dose reductions and one-fourth discontinued treatment early). Boceprevir- and telaprevir-based triple therapy has been associated with higher rates of SVR, but with higher rates of side effects, and has major drug–drug interaction issues in which the immunosuppressive regimens needs to be closely monitored and preemptively adjusted during the treatment period [59, 66]. Therefore, these triple therapies are not recommended by the recent AASLD/IDSA and EASL guidelines. The AASLD/IDSA guidance recommend that patients with recurrent HCV post-liver transplant, including those with compensated cirrhosis, be treated with all-oral DAA regimens containing sofosbuvir, ledipasvir, simeprevir, daclatasvir, and RBV, according to the genotypes. Tacrolimus or cyclosporine dose adjustments are not needed when treating with these combinations. However, careful monitoring is recommended because of the lack of safety data in this group of patients (Table 11.5). The fixed-dose combination of paritaprevir/ritonavir/ombitasvir plus dasabuvir and RBV for 24 weeks can be an alternative regimen for patients with genotype 1 in the allograft, without cirrhosis [1]. Notably, ritonavir is a strong CYP3A inhibitor, and therefore the dose of calcineurin inhibitors should be adjusted and closely monitored during the treatment. The benefit of immunosuppressive strategy on the natural history HCV recurrence has not been well elucidated, although there has been evidence suggesting a neutral or small beneficial effect of cyclosporine A, mycophenolate mofetil, and sirolimus [59, 64, 65].

HCV Infection in Patients With Human Immunodeficiency Virus (HIV) Infection

In developed countries, approximately 15–25 % of HIV-infected persons are chronically infected with HCV [67–69]. The prevalence of HIV/HCV coinfection varies markedly depending on the route of HIV acquisition, being lower among persons reporting high-risk sexual exposure (8–15 %) and higher in those reporting injection drug use (50–90 %) [68, 69]. HIV infection adversely affects the natural history of HCV, leading to increased viral persistence after acute infection, higher levels of viremia, accelerated progression to cirrhosis and ESLD, and increased risk of liver-related death [68–70]. Successful HCV eradication in HIV-infected patients not

only prevents liver disease progression, but is also associated with a reduction in the risk of antiretroviral (ARV)-induced hepatotoxicity, HIV disease progression and non–liver-related mortality [68, 69, 71, 72].

Prompt treatment for HCV should be considered in all patients with HIV/HCV coinfection; however, in patients with CD4+ cell count <200 cells/mm^3, it may be preferable to improve the CD4+ cell count by starting ARV before HCV treatment [1, 13, 14]. In the interferon era, HCV treatment in HIV-infected patients was limited due to historically low response rates, patient comorbidities, physician perception, adverse effects associated with IFN-based therapy and drug–drug interactions [1]. Treatment with PEG-IFN plus RBV, can eradicate HCV in 14–29 % of HIV-infected patients coinfected with HCV genotype 1 and 44–73 % of patients coinfected with HCV genotype 2 or 3) [73] With the availability of HCV DAAs, SVR rates have markedly improved, but treatment requires awareness of complex drug interactions between DAAs and ARV therapy (Table 11.3). The AASLD//IDSA guidance has recommended that HIV/HCV coinfected patients be treated and retreated the same as non-HIV patients, after recognizing and managing interactions with ARV (Tables 11.4 and 11.5). These recommended all-oral combination regimens are generally associated with SVR rates of >90 % and similar to that of non-HIV patients. Sofosbuvir generally has no/minimal interaction with ARV, but it is not recommended for use with tipranavir because of the potential of this drug to induce P-gp [1]. Ledipasvir can increase the concentration of tenofovir that is in ARV regimen and present risk of nephrotoxicity. Simeprevir concentration are significantly decreased when dosed with efavirenz and increased when dosed with darunavir/ritonavir [1]. Because 100 mg of ritonavir is coformulated with paritaprevir and ombitasvir, the total dose of ritonavir must be carefully considered and adjusted when using ritonavir-boosted regimen [1, 74]. The combined use of RBV and didanosine is contraindicated due to the potential for dangerous interactions resulting in mitochondrial toxicity causing hepatic steatosis, liver failure, peripheral neuropathy, pancreatitis, and lactic acidosis [75]. The combined use of RBV and zidovudine should also be avoided due to increased rate of anemia [76].

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