Hepatitis C in Hospital Medicine

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KEYWORDS
- Hepatitis C infection
- Acute hepatitis C
- Chronic hepatitis C
- Direct-acting antivirals
- Hepatocellular carcinoma

HOSPITAL MEDICINE CLINICS CHECKLIST

1. Hepatitis C is separated into acute and chronic infections. Acute infection presents with nonspecific symptoms and increased liver function tests. Chronic hepatitis C is often asymptomatic for many years.
2. Acute hepatitis C is cleared in 15% to 25% of cases, with the remainder progressing to chronic infection.
3. Untreated patients advance to cirrhosis approximately 20% of the time, and those with cirrhosis progress to hepatocellular carcinoma at a rate of 1% to 4% per year.
5. Screening is recommended once for all individuals born between 1945 and 1965. Yearly screening is recommended for patients with active risk factors for contracting the virus, such as injection drug use.
6. Risk factors for contracting hepatitis C include injection drug use, blood transfusion before 1992, receiving clotting factors for hemophilia before 1987, long-term hemodialysis, needle-stick injuries, being born to a mother infected with hepatitis C virus, incarceration, and having had tattoos in an unregulated setting.
7. Conditions that cause continued liver inflammation expedite the progression to severe fibrosis and cirrhosis. Alcohol use, human immunodeficiency virus infection, viral -hepatitides, and steatohepatitis associated with metabolic syndrome and diabetes are the most common conditions that accelerate progression.

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8. The utility of liver biopsy in the diagnosis of cirrhosis has come under scrutiny as other noninvasive measures of fibrosis, such as serologies and imaging, have improved. However, it remains the recommendation of the American Association for the Study of Liver Diseases to perform a liver biopsy when investigating the severity of fibrosis.

9. Treatment success is measured by sustained virological response (SVR). SVR is defined as undetectable viral RNA 24 weeks after completion of treatment. Patients achieving SVR are deemed cured.

10. Current treatment is recommended with a combination of direct-acting antivirals (polymerase inhibitor and protease inhibitors) and indirect-acting antivirals (interferon and ribavirin).

11. SVR rates for genotype 1, which is the most common in the United States, has been as high as 89%.

12. Several conditions are associated with hepatitis C. Mixed cryoglobulinemia is the most common medical condition associated with hepatitis C.

13. Standard precautions are recommended for medical professionals when caring for patients with hepatitis C.

14. The most common means of nosocomial transmission are reuse of syringes, drug diversion, and lapses in infection control.

DEFINITIONS

What is the definition of hepatitis C infection?

Hepatitis C virus (HCV) is an enveloped RNA virus transmitted through blood contamination. The virus causes inflammation of the liver leading to complications such as cirrhosis and hepatocellular carcinoma (HCC).¹

How is hepatitis C infection classified?

Hepatitis C is described as a silent epidemic, in large part because of the asymptomatic nature of chronic infections. Chronic hepatitis C is usually discovered by laboratory abnormalities in asymptomatic patients, several years after infection. Chronic hepatitis C infection comprises 75% of those infected.² Acute hepatitis C presents as an acute illness consisting of nonspecific complaints of nausea, anorexia, fever, malaise, and abdominal pain in conjunction with either jaundice or increased transaminase levels.³

EPIDEMIOLOGY

What is the epidemiology of hepatitis C?

Worldwide, 3% of the population is infected with hepatitis C. The most recent data suggest that the prevalence of hepatitis C in the United States is approximately 2.7 million individuals, or 1% of the population. These data were obtained from a National Health and Nutrition Examination Survey of 30,074 people, with 274 participants testing positive for chronic hepatitis C. The data were extrapolated to estimate the prevalence of the disease across the population of the United States.⁴
Two populations that were not included in the survey were the homeless and incarcerated. Given that both the homeless and incarcerated have high risk for disease, with an estimated 29% of the prison population positive for HCV, these figures likely underestimate the true prevalence of the disease.4

**What is the epidemiology of hepatitis C in inpatients?**

With respect to the inpatient population, using the Agency for Healthcare Research and Quality (AHRQ) National Inpatient Sample, 622,631 discharged patients in 2012 carried a billing diagnosis of hepatitis C. The ICD-9 (International Classification of Diseases, Ninth Revision) codes that were used to run the analysis used all codes specifically identifying hepatitis C, but excluded vague codes (eg, acute hepatitis) that could represent any of the viral hepatitides. The same evaluation done for 2002 showed the number of discharges with a diagnosis of hepatitis C to be 334,951, showing that the prevalence of hepatitis C in hospitalized patients has nearly doubled in the past 10 years (Table 1).5

**What coexisting conditions correlate with worse outcomes?**

The coexisting conditions that lead to worse outcomes for patients with HCV infection are the conditions that speed up the process of ongoing liver damage. Continued alcohol consumption leads to faster progression of fibrosis and ultimately cirrhosis. In addition, alcohol may increase the replication of HCV RNA. What remains unknown is the quantity of alcohol consumption that leads to these deleterious effects.6–8 Human immunodeficiency virus (HIV) coinfection has been shown to increase the rapidity with which cirrhosis develops, and in some cases liver disease can progress to fibrosis in as little as 2 to 8 years.6–8 Concomitant conditions leading to liver fibrosis, such as other viral hepatitides (hepatitis B virus [HBV], hepatitis A virus [HAV]), cause faster progression of disease.6–8 Metabolic syndrome and diabetes are associated with steatohepatitis, which can accelerate the progression to fibrosis. In addition, poor glucose control can decrease the effect of therapy for HCV.6–8

**What are the risk factors for hepatitis C infection?**

The largest risk factor for contracting hepatitis C is injection drug use (past or present), with 50% prevalence in that population. Injection drug use accounts for 60% of acute hepatitis C infections. Intranasal drug use is also a risk factor for transmission of HCV.6 Other risk factors include receiving a blood transfusion before 1992; receiving clotting factors for hemophilia before 1987; long-term hemodialysis; needle-stick injuries; being born to a mother infected with HCV; incarceration; and having had tattoos, particularly in an unregulated setting.6

**Table 1**

<table>
<thead>
<tr>
<th>Frequency of hepatitis C in hospitalized patients</th>
<th>2012</th>
<th>2002</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total discharges (nonneonatal, nonmaternal)</td>
<td>28,391,049</td>
<td>27,887,517</td>
</tr>
<tr>
<td>Hepatitis C diagnosis code</td>
<td>622,631</td>
<td>334,951</td>
</tr>
<tr>
<td>Prevalence (%)</td>
<td>2.2</td>
<td>1.2</td>
</tr>
</tbody>
</table>

What is the natural history of hepatitis C?

HCV infection is cleared in 15% to 25% of acutely infected patients. The remaining 75% to 85% of patients become chronically infected with HCV. Cirrhosis develops in 10% to 20% of patients chronically infected with HCV. Cirrhotics then progress to HCC at a rate of 1% to 4% per year.6

What is the risk of nosocomial transmission?

Between 2008 and 2013 there were 18 outbreaks of hepatitis C in health care–associated settings. Because of the 18 outbreaks, 228 outbreak-associated cases were identified and more than 92,550 patients were deemed at risk. There were 4 settings in which the outbreaks took place: outpatient, long-term care, hospital, and hemodialysis. Hospitals accounted for 2 outbreaks spanning 9 states and 17 facilities. There were more than 19,000 patients placed at risk, with 71 cases of infection identified. The most common causes of outbreaks across all settings were reusing syringes, drug diversion, and lapses in infection control.9

PATIENT EVALUATION AND DIAGNOSIS

What is the clinical presentation of hepatitis C?

Most patients infected with HCV are asymptomatic on presentation and are chronically infected (75%). They are most commonly diagnosed as part of a work-up of an unrelated condition or through screening. Patients who are chronically infected may also present with hepatic complications of cirrhosis at diagnosis. There are several nonhepatic manifestations of HCV infection that present and these are discussed later. Acute HCV infection presents with symptoms that are nonspecific, including malaise, nausea, fever, anorexia, and abdominal pain.6

How should patients be screened for hepatocellular carcinoma?

- A 1-time HCV screening should take place with an HCV antibody in all individuals born between 1945 and 1965.
- All active injection drug users and men infected with HIV who have sex with men should be screened once a year for HCV infection.
- Periodic testing (without a defined period) is recommended for patients with at-risk behaviors, such as patients on long-term dialysis, incarcerated individuals, and persons having received unregulated tattoos.
- Patients who are admitted to hospital and are at risk (injection drug users, men who have sex with men, patients on long-term dialysis, incarcerated individuals, and persons having received unregulated tattoos) for hepatitis C should be screened.
- Admitted patients who are at risk for infection, as well as having a nonspecific illness and increase in liver function tests (LFTs), should be evaluated for hepatitis C with an anti-HCV antibody and, if negative, an HCV viral load.
- At-risk populations and patients born between 1945 and 1965 who are noted to have an asymptomatic increase in LFTs should be screened with anti-HCV antibody testing.6,10,11
What laboratory studies are recommended for evaluation and diagnosis?

There are 2 forms of serologic testing: immunoassays and molecular assays. Immunoassays test for the presence of antibodies against HCV and are used for screening and diagnosis. Polymerase chain reaction (PCR) is used to test for the presence of hepatitis C RNA and to quantitate the viral load present in an infected patient. PCR assays are also used to discern the viral genotype in an infected patient. This information guides the agents used in treatment (Fig. 1).

Viral RNA is present within 2 weeks of exposure, whereas antibody takes 8 to 12 weeks to form. For acute HCV infection, a positive HCV antibody test in the appropriate clinical scenario in the setting of both negative immunoglobulin (Ig) M anti-HAV and IgM anti-HBc is sufficient for diagnosis. The positive HCV antibody should be followed by PCR testing for HCV RNA. If confirmed with a positive test, obtaining the genotype is essential for treatment (Table 2).

What imaging is used for evaluation?

Identifying the level of fibrosis or cirrhosis is essential in patients with HCV in order to plan treatment and monitor for complications. Imaging modalities such as ultrasonography, computed tomography, and MRI provide data about the liver, such as size, nodularity, fatty infiltration, portal flow, and spleen size, but none are able to specify the degree of fibrosis or cirrhosis.6

Who requires a liver biopsy?

Evaluation for fibrosis in patients with chronic hepatitis C infection is imperative because it dictates treatment. Liver biopsy has long been the gold standard for evaluation of fibrosis; however, there are several noninvasive modalities being investigated to

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*Potential for false negative anti-HCV antibody in immune-compromised patients

Fig. 1. Patient screening algorithm. HCV, hepatitis C virus; PCR, polymerase chain reaction.
evaluate for fibrosis. Although liver biopsy is usually well tolerated, it is invasive. The complications that are associated include abdominal pain (25%), bleeding (0.05%–5.3%), and a mortality of less than 0.15%. Variability in staging exists between lobes of the liver, further complicated by intraobserver and interobserver variability. Further, inadequacy of sample size can lead to misinterpretation of the level of fibrosis.6

Noninvasive markers of fibrosis are separated into 2 categories: biomarkers and imaging modalities. Indirect biomarkers (eg, platelets, GGT, aspartate aminotransferase [AST], alanine aminotransferase, age, cholesterol, and gamma globulin) can be used to develop a score that predicts the severity of cirrhosis. An example includes the AST/Platelet Ratio Index score. Direct markers are also used. The direct markers include age, sex, serum haptoglobin, alpha2-macroglobulin, apolipoprotein A1, GGT, hyaluronic acid, TIMP-1, PIIINP, prothrombin index, AST, blood urea nitrogen, and total bilirubin.6

In addition, there are imaging modalities available to measure the stiffness of the hepatic tissue. The most notable of these modalities is transient elastography, which uses elastic waves and ultrasound to derive a score to correlate with the level of fibrosis present. Transient elastography has a positive predictive value and negative predictive value of 90% when using a cutoff of 17.6 kPa as a predictor of cirrhosis.12

The current recommendation from the American Association for the Study of Liver Diseases (AASLD) is to obtain a liver biopsy when evaluating for fibrosis. Liver biopsy is generally considered in patients with chronic hepatitis C infection in order to determine fibrosis stage for prognostic purposes or to make a decision regarding treatment. In addition, the AASLD acknowledges the potential benefits of using noninvasive modalities to evaluate for advanced fibrosis and cirrhosis in chronic hepatitis C, but do not recommend those tests in place of a liver biopsy.6

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Interpreting laboratory testing</th>
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</thead>
<tbody>
<tr>
<td>Anti-HCV</td>
<td>HCV RNA</td>
</tr>
<tr>
<td>Positive</td>
<td>Positive</td>
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<tr>
<td>Positive</td>
<td>Negative</td>
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<td>Negative</td>
<td>Positive</td>
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<td>Negative</td>
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TREATMENT

How is treatment success evaluated?

SVR is the most important marker and is defined as absence of virus detected in the serum 24 weeks after completion of treatment. Patients who achieve SVR are considered cured of hepatitis C. Although late relapse has been reported, it seems to be rare. Rapid virologic response, which is the absence of virus at 4 weeks of treatment, is a positive predictor of achieving SVR. Early virological response (EVR) is defined as greater than 2-log decrease or complete absence of virus at 12 weeks of treatment. Failure to attain EVR is the best predictor of not achieving SVR.6

Even if SVR is achieved, this does not eliminate all morbidity and mortality related to hepatitis C. Patients who are cirrhotic still carry the risk of developing HCC. It is possible that, as more cirrhotic patients are cured and survival increases, the rate of HCC will increase.

What is the goal of treatment?

The goal of treatment of HCV infection is to achieve SVR. As described earlier, SVR is determined based on the presence or absence of the virus and its RNA. Unlike HIV, the hepatitis C genome does not get integrated into the host cell DNA, and therefore SVR is considered to indicate cure. With specific targeting, eradication of the virus from infected cells allows cure rather than simple suppression.

What are contraindications to treatment?

There are several contraindications to treatment protocols using interferon (IFN) and ribavirin (RBV). The contraindications are largely caused by the complications and side effects of the agents. The contraindications are listed in Box 1.

There are several circumstances that are not absolute contraindications, although special consideration is needed when treatment is being discussed. Patients who are actively abusing illicit drugs or alcohol but are willing to undergo treatment of their drug dependence in a substance abuse program or alcohol

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### Box 1
Contraindications to treatment

- Major and/or uncontrolled depressive illness
- Solid organ transplant
- Autoimmune hepatitis
- Autoimmune conditions exacerbated by peginterferon and RBV
- Untreated thyroid disease
- Pregnancy (or refusal to use contraception)
- Concurrent medical disease: severe hypertension, heart failure, significant coronary heart disease, poorly controlled diabetes, chronic obstructive pulmonary disease
- Younger than 2 years old
- Hypersensitivity to drugs used to treat HCV
support program should come under consideration after abstinence is achieved for 6 months and with close observation by a specialist. Patients with a failed prior treatment (nonresponder and relaper) with IFN with or without RBV or peginterferon monotherapy are a population of special interest with current treatment regimens (including direct-acting antivirals) because of the hopes of achieving high cure rates. Other special patient populations that require further consideration include patients with chronic renal disease (dialysis dependent or not), decompensated cirrhotics, and liver transplant recipients. Patients with acute hepatitis C and coinfection with HIV are discussed later.6

What drugs are currently used for treatment?

Therapies for HCV infection are indirect-acting antivirals and direct-acting antivirals. Indirect-acting antivirals include IFN-α2a and RBV. IFN-α2a stimulates the IFN-1 receptor inducing the JAK/STAT pathway, which invokes the release of antiviral mediators across several cell types.14 RBV is an antiviral agent that induces mutations in the genome of several RNA viruses, although the specific mechanism of action is unknown.15

Direct-acting antivirals are recently developed drugs that specifically target hepatitis C. These drug classes include protease inhibitors and polymerase inhibitors. Protease inhibitors (eg, boceprevir, telaprevir, simeprevir) disrupt the nonstructural proteins essential in the life cycle of hepatitis C; namely, proteases NS3/4A. These drugs used in monotherapy are susceptible to selection of resistant strains of HCV. When combined with peginterferon alfa and RBV, the SVR rates dramatically increase. Polymerase inhibitors (sofosbuvir) terminate transcription of the viral RNA and thereby disrupt elongation of transcription products. Because the site of action (the catalytic site) is highly conserved, this protects the polymerase inhibitors from resistance patterns and strains.16

Has treatment of chronic hepatitis C changed recently?

In May of 2011, the US Food and Drug Administration (FDA) approved the protease inhibitors telaprevir and boceprevir in treatment of HCV as part of triple therapy (in combination with IFN and RBV). The treatment combinations increased SVR compared with IFN and RBV alone. However, the protease inhibitors quickly lost favor because sofosbuvir, a polymerase inhibitor, was approved in December 2013. Sofosbuvir combined with IFN and RBV brought a shorter treatment duration (12 weeks), higher SVRs (89%), and fewer side effects than standard therapy using RBV plus IFN, or RBV plus IFN plus telaprevir or boceprevir. Note that telaprevir and boceprevir are no longer recommended in any treatment regimen.17–19 In October 2014, ledipasvir-sofosbuvir was approved by the FDA for the treatment of genotype 1 chronic hepatitis C infection. This combination of ledipasvir, an HCV NSSA protein inhibitor, with sofosbuvir is administered in a once-daily dose and resulted in greater than 97% SVR in treatment-naive patients. It offers the first approved regimen that does not require administration with IFN or RBV. Because of the recent approval, at the time of submission of this article, ledipasvir-sofosbuvir has not yet been incorporated into the AASLD treatment guidelines.

The treatment of chronic hepatitis C is still evolving rapidly as the development of new pharmaceuticals continues beyond the newest treatment recommendation, which includes sofosbuvir. The current recommendations for treatment depend on...
multiple factors, the most paramount of which are HCV genotype and the patient’s ability to take IFN. The current AASLD recommended therapies are listed based on genotype in Table 3.

**What is the treatment of acute hepatitis C?**

Treatment of acute hepatitis C infection is only to be considered in subset populations that would benefit from early intervention. Patient populations that may benefit from early treatment include intravenous drug users who have a high risk of further transmitting the virus, compensated cirrhotics with risk of complications of superinfection, surgeons, and patients at risk for being lost to follow-up. If early treatment were pursued, the same regimen as for chronic HCV in the same clinical scenario is recommended. One caveat is that IFN-sparing regimens have not been studied in acute infection, and are not recommended for early treatment.

If treatment of acute HCV is sought, it must occur by 12 weeks of inoculation (if known). IFN-based treatments have shown SVR rates in the 80% to 85% range when treatment is initiated by 12 weeks of infection. This value decreases to the 60% range when delayed until weeks 16 to 24. Waiting until 12 weeks allows for natural clearance of the virus. Given that 20% to 50% of patients clear the infection without intervention, and the complications are largely a result of chronic infection, treatment is withheld until infected patients have a chance to clear the infection on their own to avoid the risk of treatment. If a patient is going to clear the infection, it is usually cleared by 12 weeks; however, it can take up to 20 weeks.

The current recommendation of the AASLD/Infectious Diseases Society of America for most populations of patients infected with HCV is to wait 6 months before initiation of treatment. After 6 months of persistent viremia, only 11% of patients spontaneously clear the infection. At 6 months, infected patients are considered to be chronically infected. Chronic infection allows IFN-sparing treatments to be used. These

| Genotype 1 | Daily sofosbuvir and weight-based RBV plus weekly PEG for 12 wk | Daily sofosbuvir plus simeprevir with or without weight-based RBV (IFN ineligible) |
| Genotype 2 | Daily sofosbuvir and weight-based RBV for 12 wk | None |
| Genotype 3 | Daily sofosbuvir and weight-based RBV for 24 wk | Daily sofosbuvir and weight-based RBV plus weekly PEG for 12 wk |
| Genotype 4 | Daily sofosbuvir and weight-based RBV plus weekly PEG for 12 wk | Daily sofosbuvir plus weight-based RBV for 24 wk (IFN ineligible) |
| Genotype 5 | Daily sofosbuvir and weight-based RBV plus weekly PEG for 12 wk | None |
| Genotype 6 | Daily sofosbuvir and weight-based RBV plus weekly PEG for 12 wk | Daily weight-based RBV plus weekly PEG for 48 wk |

*Table 3: Current treatment recommendations*

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**Table 3: Current treatment recommendations**

| Genotype 1 | Daily sofosbuvir and weight-based RBV plus weekly PEG for 12 wk | Daily sofosbuvir plus simeprevir with or without weight-based RBV (IFN ineligible) |
| Genotype 2 | Daily sofosbuvir and weight-based RBV for 12 wk | None |
| Genotype 3 | Daily sofosbuvir and weight-based RBV for 24 wk | Daily sofosbuvir and weight-based RBV plus weekly PEG for 12 wk |
| Genotype 4 | Daily sofosbuvir and weight-based RBV plus weekly PEG for 12 wk | Daily sofosbuvir plus weight-based RBV for 24 wk (IFN ineligible) |
| Genotype 5 | Daily sofosbuvir and weight-based RBV plus weekly PEG for 12 wk | None |
| Genotype 6 | Daily sofosbuvir and weight-based RBV plus weekly PEG for 12 wk | Daily weight-based RBV plus weekly PEG for 48 wk |

*Abbreviation: PEG, peginterferon.*

*Adapted from American Association for the Study of Liver Diseases (AASLD)/Infectious Diseases Society of America (IDSA)/International Antiviral Society-USA (IAS–USA). Recommendations for testing, managing, and treating hepatitis C. Available at: http://www.hcvguidelines.org. Accessed April 24, 2014.*
treatments are tolerated well and achieve a high SVR without subjecting the patient to the duration and side effects of IFN treatment.\(^\text{17}\)

**What are the common complications of treatment that may be seen in hospitalized patients?**

The most common side effects of treatment continue to be those associated with IFN therapy, including depression, fatigue, influenzalike symptoms, nausea, and insomnia. Serious adverse events have included anemia, thrombocytopenia, neutropenia/leukopenia, and serious infections related to neutropenia.\(^\text{16,20}\)

**Does cirrhosis affect treatment?**

There are data across several studies that show that patients with severe fibrosis and cirrhosis have decreased rates of SVR compared with patients who do not. When treated with sofosbuvir, peginterferon, and RBV, patients with genotype 1 HCV and cirrhosis have decreased rates of SVR compared with patients without cirrhosis (80% and 92%, respectively).\(^\text{20}\)

**Can nonresponders to prior treatment be treated again?**

There are limited data on prior treatment (IFN/RBV) of nonresponders with regard to the newest treatments and, in particular, sofosbuvir plus IFN and RBV. Preliminary data suggest that nonresponders have similar rates of SVR to patients with factors that predict poor response to IFN. In addition, it was recently shown in a prospective study in patients with recurrent disease after liver transplantation that treatment with sofosbuvir and RBV had an SVR of 70%\(^\text{17,21,22}\).

**How does HIV coinfection alter treatment?**

HIV/HCV coinfection has serious implications because of the rapidity with which the disease progresses. Liver fibrosis progresses more quickly than in patients without HIV infection and cirrhosis occurs earlier in the disease course. At slightly more than 23 years of HCV infection, cirrhosis is present in approximately 10% of patients who are HCV monoinfected. In the same study, at 22 years of HCV infection, cirrhosis was present in 27% of patients coinfected with HIV/HCV.

This finding has implications for morbidity, mortality, and treatment outcomes given that morbidity and mortality are higher for coinfected patients. Treatment with sofosbuvir and RBV showed excellent SVRs in genotypes 1 to 3 in treatment-naive patients coinfected with HIV/HCV. The effect of cirrhosis across genotypes decreased SVR to \(\sim 60\)% compared with those without cirrhosis (\(\sim 80\)%).

The recommended treatment of sofosbuvir, IFN, and RBV is being tested in an ongoing trial in patients coinfected with HIV/HCV, with preliminary SVR12 (sustained virologic response 12 weeks after induction) results for genotype 1 of 89\%.\(^\text{7,8,17,23,24}\)

**PROGNOSIS**

**What is the prognosis of treatment of hepatitis C infection?**

With the new treatment regimens available, approximately 90% of treated patients achieve SVR. With ongoing drug development and treatment optimization, it is reasonable to believe that SVR rates close to 100% are achievable in the near future. The
unknown complications include the long-term morbidity associated with a longer survival with cirrhosis or severe fibrosis. HCC rates in this setting will be interesting to investigate.

**What are extrahepatic complications of hepatitis C?**

There are at least 36 extrahepatic conditions associated with HCV, of which mixed cryoglobulinemia is the most frequent with a prevalence as high as 44% in patients with chronic HCV infection (Box 2). The most common physical manifestation of mixed cryoglobulinemia is palpable purpura. The classic triad of palpable purpura, arthralgias, and weakness described in the 1960s is rarely seen. The specific autoantibodies that make up mixed cryoglobulinemia are a heterogeneous population and vary across the population, which makes it difficult to prove that the downstream effects and manifestations are caused by cryoglobulins.

Membranoproliferative glomerulonephritis (MPGN) and nephrotic syndrome are renal manifestations that are associated with HCV infection. This manifestation is thought to be caused in part by the deposition of cryoglobulins in the glomeruli. The prevalence of MPGN in patients with type II cryoglobulinemia is approximately 30%.

In contrast, porphyria cutanea tarda has been linked to HCV infection; however, there has been no evidence of a causal relationship because HCV does not decrease the activity of hepatic uroporphyrinogen decarboxylase. Note that alcohol does decrease its activity, and alcoholism is a common comorbid condition in these patients.

Other notable conditions associated with HCV infection include diabetes mellitus, rheumatoid arthritis, and keratoconjunctivitis sicca.

**CLINICAL GUIDELINES**

**What precautions should health care workers take in caring for patients with hepatitis C?**

The US Centers for Disease Control and Prevention recommends standard precautions when caring for patients with hepatitis C infection. Standard precautions include routine hand hygiene with alcohol-based hand rub or soap and water, and using personal protective equipment in the appropriate settings. Examples of personal protective equipment include wearing gloves when there is risk of blood exposure, mucous membranes, nonintact skin, or contaminated equipment, and wearing a gown and protective face shield during appropriate procedures or if there is risk for blood spatter.

**DISCHARGE INSTRUCTIONS**

**What are the recommendations for reducing transmission?**

Transmission of HCV happens through blood exposure. The recommendations to reduce transmission focus on limiting exposures to potential sources of contaminated fluids. Sharing toothbrushes, dental equipment, and shaving equipment should be avoided. Patients should cover bleeding wounds in order to prevent exposure of their blood to others. Abstinence from illicit drugs is recommended strongly, and if patients continue to abuse injection drugs they should be counseled on the risks of using shared paraphernalia such as syringes, needles, water, and cotton. Similarly, they should be educated on clean techniques as well as safe disposal of equipment if they are going to continue to abuse injection drugs. Donation of bodily fluids such as blood, organs, and semen should be discouraged. In addition, with regard to sexual
Box 2

Conditions associated with HCV infection

Antiphospholipid syndrome
Aplastic anemia
Autoimmune hemolytic anemia
Autoimmune thyroiditis
Chronic fatigue syndrome
Behçet syndrome
Carotid atherosclerosis
CREST syndrome
Dermatomyositis
Diabetes mellitus
Fibromyalgia
Guillain-Barré syndrome
Hypertrophic cardiomyopathy
Hypocholesterolemia
Idiopathic pulmonary fibrosis
Idiopathic thrombocytopenic purpura
IgA deficiency
Lichen planus
Mucosa-associated lymphoid tissue lymphoma
Membranoproliferative glomerulonephritis
Membranous glomerulonephritis
Mixed cryoglobulinemia
Mooren corneal ulcers
Multiple myeloma
Non-Hodgkin lymphoma
Neurocognitive impairment
Pancreatitis
Polyarteritis nodosa
Polymyositis
Porphyria cutanea tarda
Rheumatoid arthritis
Sialadenitis
Sjögren syndrome
Systemic lupus erythematosus
Uveitis
Waldenström macroglobulinemia

practices, patients infected with HCV generally do not need to revise sexual practices if they are in a monogamous relationship. They should be informed that the risk of sexual transmission is low, although safe sex practices are recommended for all infected patients, with particular focus on men who have sex with men, and patients with multiple sexual partners.  

**What are the recommendations for reducing progression of disease?**

There are several recommendations that focus on reducing the risk of progression of disease. Abstinence from alcohol is critical given the detrimental effects of ongoing alcohol use. Adherence to exercise, dietary modifications, medication compliance, and glucose control can have positive impacts on slowing the progression of disease. In addition, vaccinations against HAV and HBV to prevent coinfection are strongly recommended.  

**PRACTICE IMPROVEMENT**

The focus of practice improvement should start with properly identifying at-risk populations and screening them appropriately. Once infection is identified, follow-up with specialists (infectious diseases or hepatology) for further investigation should be established. Given the advances in therapy, intervention and treatment should be sought more readily. Hospitalists have the ability to improve identification of patients infected with HCV and therefore to affect the disease course.

Hospitalists caring for established patients infected with HCV should review with the patient how much work-up has been performed, whether they have been treated, and whether they are under the care of a specialist. If no treatment or work-up has taken place, follow-up with the appropriate physicians to address potential treatment options should be established. If a patient is undergoing treatment, ensuring that the patient is adhering to the correct treatment regimen while hospitalized (when possible) is important.

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