Chronic Hepatitis C Virus Infection

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Chronic hepatitis C virus (HCV) infection is a common worldwide problem. The infection may progress to cirrhosis with the subsequent development of complications such as ascites, encephalopathy, variceal bleeding, and hepatocellular carcinoma. Thus, early detection and therapy is of great importance. There has been substantial progress in understanding various aspects of HCV infection, including the virology, epidemiology, natural history of chronic infection, and medical therapy. The objective of this article is to provide relevant clinical information regarding the contemporary approach to patients with chronic HCV infection.

Virology

Hepatitis C virus is an RNA virus and a member of the Flaviviridae family. The RNA viruses have high mutation rates and have evolved different genotypes of HCV based on nucleotide sequence heterogeneity. There are 6 known genotypes with genotype 1 (75%), genotype 2 (approximately 10%), and genotype 3 (approximately 10%) being the most common in the United States. There is little difference in the mode of transmission or natural history of infection among the different genotypes. However, there is a large difference in response to interferon alfa-based medical regimens among the genotypes. It is thus important to determine the genotype before starting medical therapy.

An individual with chronic HCV infection typically has only 1 genotype.

Mutations within an individual continue on an ongoing basis. This leads to the development of numerous subpopulations of HCV with slight genomic differences called quasi species. The presence of quasispecies likely allows HCV to elude immune system-mediated clearance and presents challenges for development of effective medical therapy.

Most of the HCV genome codes for nonstructural enzymatic proteins necessary for viral processing and replication. A serine protease, helicase, and RNA-dependent RNA polymerase are required for HCV to multiply and are targets for future drug development.

Epidemiology

Hepatitis C virus infection is a common problem in the United States with an estimated prevalence rate of 1.8%, of which approximately 75% are thought to have chronic infection (approximately 2.7 million people). The number infected may be underestimated because high-risk groups (incarcerated, institutionalized, and homeless persons) were not included in prevalence studies. Although there are currently many new diagnoses of HCV infection, the incidence of new cases has markedly declined in recent years. This is likely due to screening of the blood supply and safer needle practices among intravenous drug users. The majority of new diagnoses of HCV infection relate to remote infection.

Hepatitis C virus infection is primarily transmitted by percutaneous exposure. Studies of patients with chronic HCV infection indicate that approximately 65% have a history of intravenous drug use. Approximately 15% received blood transfusions before 1989 when the first diagnostic test for HCV was developed and subsequently used for screening the blood pool. Small numbers of patients acquire HCV by iatrogenic exposure (unsafe injection practices and lack of adherence to universal precautions such as in dialysis centers), nosocomial exposure (needle stick injuries), intranasal drug use, spousal transmission, and vertical transmission. Approximately 10% of patients deny known transmission risk factors. Hepatitis C virus infection is not spread by casual contact, including hugging, kissing, or sharing food utensils. Spouses of patients with chronic HCV infection have a slightly increased prevalence of infection than would otherwise be expected. However, whether sexual transmission occurs is controversial. Indirect evidence suggests that HCV infection may be transmitted sexually. This evidence includes a higher prevalence in people who have multiple sexual partners, men who have a history of sex with men, and persons with sexually transmitted diseases. Such groups may have higher frequencies of other transmission risk factors, such as intravenous and intranasal drug use, which confound assessment of possible sexual transmission. Evidence against sexual transmission includes the minimally increased prevalence of HCV infection in those involved in monogamous relationships.

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mous relationships with individuals with HCV infection despite the com-
nonality of sexual intercourse. Alternatively, transmission by unrecog-
nized percutaneous exposure could explain spousal transmission. The Cen-
ters for Disease Control and Prevention does not recommend changing
sexual practices (ie, using condoms) to prevent transmission if one member of
a monogamous couple has HCV infection. The current data suggest that if
sexual transmission occurs, it is very uncommon. Patients should be ad-
vised to limit percutaneous exposure by not sharing razor blades, nail clippers,
or toothbrushes.

Regarding vertical transmission, HCV transmission occurs in approximately
3% to 7% of infants born to mothers with active HCV. Approximately 50%
of infants eradicate HCV infection. A significant number of infected chil-
dren eradicate HCV by age 2 years without intervention. Transmission from an
infected mother to the fetus cannot be prevented. There is no role for cesar-
ean delivery and immune globulin administra-
tion to the infant is ineffective. Medical therapy of HCV infection
during pregnancy is contraindicated. Breastfeeding is not contraindicated,
assuming that there is no damage to the nipple.

Diagnostic Testing

The initial diagnostic test for HCV infec-
tion is an enzyme immunoassay, a test that detects antibodies to multiple
HCV antigens (HCV enzyme immuno-
assay). The enzyme immunoassay tests are highly sensitive and specific. The
positive predictive value is high in pa-
tients with risk factors for HCV infec-
tion acquisition. There is currently very
little use for recombinant immuno-
blot assay testing because the enzyme
immunoassay is improved.

Hepatitis C virus RNA by polymer-
ase chain reaction or branched chain
DNA assay detects the virus itself and
is commercially available. The qualita-
tive test detects serum HCV at low
levels and confirms the presence of
active infection. This is particularly im-
portant before performing diagnostic
liver biopsy or commencing medical
therapy. The quantitative test deter-
mines the viral load. Determination of
viral load before beginning medical
therapy is necessary because early stop-
ing rules depend on the decrement
in viral titers while receiving ther-
apy. The HCV genotype determines the
likelihood of response and the opti-
mal length of medical therapy, and HCV
genotype testing must be performed in
all patients in whom medical therapy
is contemplated.

Natural History

The majority of acute cases are asymp-
omatic and patients rarely know when
they acquired HCV infection. Many
patients with chronic infection are
asymptomatic. Nonspecific symp-
toms such as fatigue, vague right up-
per quadrant discomfort, and pruritus
may be noted. Thus, HCV infection is
currently diagnosed several decades af-
after acquisition on routine blood test-
ing or after blood donation.

Not all patients progress to cirrho-
sis. In fact, approximately 25% of pa-
tients with HCV infection will have
hepatic fibrosis that evolves into cirrho-
sis. The other 75% have varying
degrees of hepatic inflammation, al-
though fibrosis does not develop or if
present does not progress. The aver-
age duration of infection before the on-
set of cirrhosis is 20 years, but the
range is wide, and HCV infection may
be present for 50 years before the iden-
tification of cirrhosis.

Factors that contribute to the de-
velopment of cirrhosis are unclear. Ge-
etic factors likely play a leading role.
Alcohol consumption is a major con-
tributor to the development of cirrho-
sis, and patients with HCV infection
should be advised to discontinue alco-
hol use. Obesity may also contribute
to the development of fibrosis. Weight
loss is advisable for obese patients.

The magnitude of serum aminotrans-
ferase elevations does not correlate with
inflammatory activity or the presence of
fibrosis. Viral load also does not cor-
relate with presence of fibrosis. Because
serum biochemical markers of hepatic
fibrosis have not proven to be reliable in
predicting the severity of hepatic inflam-
mation or fibrosis, liver biopsy is the only
way to assess disease severity. Biopsy
provides important information regard-
ing whether to initiate medical therapy
and whether to persist if therapy is poorly
tolerated. Unless there is a contraindi-
cation, liver biopsy should be per-
formed in patients for whom medical
therapy is contemplated.

In the setting of cirrhosis, the annual
incidence of hepatocellular carcinoma
ranges from 1% to 4%. Surgical therapy
(resection or liver transplantation) of he-
patocellular carcinoma offers the only
hope for cure; therefore, hepatocellu-
lar carcinoma must be identified early
before vascular invasion and meta-
sis. For patients with cirrhosis in whom
surgery is an option, screening for he-
patocellular carcinoma should be un-
dertaken. Although the optimal screen-
ing regimen is unknown, semiannual
visualization of the liver (using ultra-
sound, triphasic computed tomogra-
phy scan, or magnetic resonance imag-
ing with gadolinium) is prudent.

Extrahepatic Manifestations

Extrahepatic manifestations of HCV in-
fec tion include mixed cryoglobulinemia
(occasionally associated with mem-
branoproliferative glomerulonephritis
or B-cell lymphoma), porphyria cu-
tanea tarda, lichen planus, seronegative
arthritis, and certain neurological con-
ditions. These conditions are uncom-
mon. Recognition of the association of
HCV infection with these disorders is
important so that appropriate HCV test-
ing can be undertaken. If concomit-
ant HCV infection is present, medical
therapy of HCV infection often results
in improvement in the extrahepatic
condition.

Medical Therapy

Rapid advances in medical therapy now
allow clearance of HCV in the majority
of patients. Current therapeutic
alternatives, however, have numerous
adverse effects. A decision about whether
to treat must be made on an individual
basis, taking into account patient motivation, severity of disease, likelihood of attaining a response, and contraindications to therapy. The HCV RNA level and HCV genotype must be obtained before starting medical therapy. Serum HCV RNA testing is the gold standard to determine effectiveness of medical therapy. Serum alanine aminotransferase is less useful. A complete end-treatment response occurs if HCV RNA is undetectable at the end of medical therapy. A sustained response occurs if HCV RNA is undetectable 24 weeks after medication discontinuation. Chances of subsequent relapse are remote.26

The current standard of care for treatment involves use of pegylated interferon alfa 2a (180 µg per week) or 2b (1.5 µg/kg per week) in combination with ribavirin.24,25 Pegylated interferon alfa is administered by subcutaneous injection once weekly. Ribavirin is administered orally in divided doses. Sustained response rates of 54% to 56% are to be expected. Patients with genotype 1 have sustained response rates of 42% to 46% and must receive a 48-week course of medical therapy to optimize chances of attaining a sustained response.24,25,27 Patients with genotype 2 or 3 have sustained response rates of 78% to 82% and must receive only a 24-week course of medical therapy (Figure).24,25,27 Ribavirin should be dosed by weight (1000 mg/d if <75 kg and 1200 mg/d if ≥75 kg) for genotype 1, whereas 800 mg/d is sufficient for genotype 2 or 3 regardless of weight.27

Early Stopping Rules
Identification of patients who will not respond early in therapy allows for the discontinuation of the medication in nonresponders. If HCV RNA titers (quantitative) have not declined by more than 2 logs by week 12 of therapy, less than 2% of those in treatment will subsequently attain a sustained re-

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**Figure.** Treatment Algorithm for Chronic Hepatitis C Virus Infection

**INITIAL EVALUATION**

**MEDICAL THERAPY**

**FOLLOW-UP AT 24 WEEKS AFTER MEDICATION DISCONTINUED**

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Box. Common Adverse Effects and Contraindications to Therapy for Chronic Hepatitis C Virus Infection

Common Adverse Effects
Pegylated interferon alfa 2a and 2b
- Fatigue, headache, myalgias, fever and chills, insomnia, nausea, anorexia, weight loss, alopecia, irritability, depression, injection site reaction, autoimmune disease exacerbation (eczema, psoriasis, thyroid disease [hypothyroid and hyperthyroid], other), neutropenia, thrombocytopenia

Ribavirin
- Cough, shortness of breath, rash, nausea, anorexia, weight loss, hemolytic anemia, teratogenicity

Contraindications to Treatment
Decompensated liver disease, pregnancy, active autoimmune disease, severe psychiatric disease (particularly depression), hemolytic anemia, uncontrolled medical disease, poorly controlled diabetes mellitus, seizures, coronary artery disease, chronic obstructive pulmonary disease, heart failure

Consequences of Nonadherence
Nonadherence is very little chance of attaining a sustained response.28 Thus, medical therapy should be discontinued. Viral load testing must be performed by the same assay and laboratories must process samples appropriately if viral load testing is used to discontinue medications at week 12 of therapy. At week 24, HCV RNA must be undetectable (qualitative) or there is very little chance of attaining a sustained response. If HCV RNA is detectable at week 24, medical therapy should be discontinued (Figure).29

Adverse Effects and Contraindications
Adverse effects of pegylated interferon alfa 2a and 2b are numerous, and the incidence is quite high (Box).30,31 Flu-like symptoms (fatigue, fever, malaise, nausea, myalgias, and arthralgias) are quite troublesome. Hydration and liberal use of acetaminophen and anti-inflammatory medications may be helpful; however, if the patient consumes alcohol regularly or if more anti-inflammatory medications are taken than is recommended, there is risk of liver damage from acetaminophen. Sleep disturbance is common and may contribute to the fatigue. Neuropsychiatric effects including anxiety, increased irritability, and depression are particularly problematic. Use of antidepressants may be necessary to improve mood during therapy. Alopecia is not uncommon. Fortunately, hair grows back after discontinuation of the medications. Thyroid function and serum neutrophil and platelet counts should be monitored throughout pegylated interferon alfa therapy.

Ribavirin may cause hemolysis, which is occasionally profound. Hemoglobin levels must be followed carefully throughout therapy. Ribavirin dose reduction helps mitigate the anemia of hemolysis, although a lower ribavirin dosage decreases chances of attaining sustained response. Erythropoietin is effective in maintaining desirable hemoglobin levels and ribavirin dosage in patients with significant hemolysis.30 Rashes are quite common. There is some relief with topical corticosteroid creams or ointments. Nausea and weight loss are not uncommon but tend to resolve with discontinuation of ribavirin. A sensation of dyspnea and a nonproductive cough have also been associated with ribavirin use. Ribavirin is contraindicated in patients with renal insufficiency and is teratogenic.

Adherence
Patients who receive more than 80% of pegylated interferon alfa 2b and ribavirin for more than 80% of the treatment course have optimal sustained response rates.31 Efficient management of adverse effects allows improved adherence and offers maximal benefit of therapy. Aggressive adverse effect management, including a patient workbook and reference manual for the prescribing physician, and supportive nursing intervention by telephone using cognitive behavioral therapy decrease the dropout rate (week 24) and improves quality of life (through week 12) while receiving therapy.32

Whom to Treat?
Improvements in sustained response rates and better adverse effect management have increased the indications for therapeutic intervention. Patients without contraindications should be considered for therapy.33 Randomized clinical trials have not been performed showing that successful therapy decreases liver transplantation rates or improves survival. Nevertheless, individuals who should strongly be considered for therapy include patients with fibrosis or cirrhosis identified on liver biopsy, patients with genotype 2 or 3, patients with symptoms (eg, fatigue), and those with extrahepatic manifestations.

It is unclear if therapy is necessary for asymptomatic patients with genotype 1 and no hepatic fibrosis. Therapeutic decisions in this population, particularly in young adults or in highly motivated individuals, should be made on an individual basis.

Future Investigation
Despite rapid progress in the understanding of many aspects of HCV infection, much remains unknown. Regarding therapy, studies involving special populations, such as children, the elderly, patients with renal insufficiency, HCV and human immunodeficiency virus coinfection, and compensated cirrhosis, are ongoing. Studies are under way to determine if long-term maintenance therapy for patients with extensive fibrosis or cirrhosis is beneficial without viral clearance. New classes of promising medications are under development.34 Putative antifibrotic medications such as
interferon gamma are undergoing evaluation. The RNA polymerase, helicase, and protease inhibitors are in early-phase trials. Vaccine development programs are also under way. There is reason for hope that the remarkable evolution of effective therapies for HCV infection will continue.

REFERENCES