Professional Gaps

Most anesthesiologists are unaware of the effects of hepatitis C virus (HCV) transmission and the potentially severe consequences associated with the infection. The committee has deemed anesthetic implications of HCV infection and methods to prevent disease transmission to be essential information.

Learning Objectives

At the end of this activity, the participant should be able to:

1. Understand the epidemiology and pathophysiology of HCV infection.
2. Identify patients that should be screened for the infection.
3. List the appropriate tests to perform once a patient has been diagnosed with HCV infection.
5. Describe the preferred drug treatment regimen for patients infected with the infection and the side effects and contraindications to therapy.
6. List complications of the infection.
7. Describe appropriate precautions to prevent HCV transmission.
8. Outline means to prevent postoperative complications in patients with HCV infection.
9. Identify new developments in drug therapies to treat the infection in patients who fail initial treatment.
10. Present an anesthetic plan suitable for patients with HCV infection.
Case History

A 62-year-old man presented for open repair of a ventral hernia that had developed as a consequence of an emergency exploratory laparotomy he had undergone 30 years previously following a motor vehicle accident. Medical history included gout, for which he took allopurinol, and obesity (body mass index [BMI], 33 kg/m²). He was a lifelong nonsmoker and consumed no more than 2 alcoholic beverages per night.

Routine preoperative lab tests demonstrated mildly elevated aspartate aminotransferase (AST) and alanine aminotransferase (ALT), at 66 IU/L and 88 IU/L, respectively. Other chemistries, hematocrit, white blood cell, and platelet counts were normal, but the international normalized ratio (INR) was 1.2. In light of elevated AST and ALT levels, a hepatitis panel was drawn. The enzyme immunoassay test for hepatitis C antibodies was positive. Recombinant immunoblot assay confirmed the diagnosis, and quantitative polymerase chain reaction (PCR) for hepatitis C RNA revealed a viral load of 885,000 IU/mL, genotype 1a.

Epidemiology

HCV is a blood-borne infection caused by a single-stranded RNA flavivirus. The worldwide prevalence of HCV infection is about 3% (130 million to 180 million individuals). In the United States, approximately 1.3% (3.2 million people) of the adult population is infected with HCV. HCV infection is the leading cause of death from liver disease and the main indication for liver transplant in the United States.

HCV infection is most prevalent among current or former users of injection drugs, resulting from the sharing of needles and other drug paraphernalia. In adults with a history of injection drug abuse, the prevalence of HCV infection is more than 45% and may be as high as 90% in older drug abusers. The prevalence of HCV infection also is considerably elevated among patients on hemodialysis, estimated at 8.9% to 14.9% in the United States. Individuals who received blood transfusions or solid organ transplants prior to 1992 are at increased risk for HCV infection, as routine HCV testing of donated blood products did not occur before that time. Given current testing methods, blood transfusion in the United States has a very low risk for HCV transmission—less than 1 case per 2 million units transfused.

Sexual intercourse is an inefficient means of HCV transmission, but the presence of HCV infection is significantly higher in people with multiple sexual partners. People who are infected with HCV are advised to use condoms during sex and not to share razors, toothbrushes, or other devices that may become contaminated with blood. Maternal-to-fetal HCV transmission also is uncommon, estimated to account for approximately 5% of cases. Although most infants with vertically acquired HCV remain chronically infected, their disease progression tends to be mild. HCV is not transmitted in breast milk or saliva.

Pathophysiology

Acute infection with HCV is asymptomatic in 60% to 70% of patients. In the remainder, symptoms are non-specific and include fatigue, nausea, abdominal pain, and anorexia. HCV RNA typically can be
identified as early as 2 weeks after acute exposure, and onset of symptoms generally occurs within 4 to 12 weeks. Antibodies to HCV typically appear 8 to 12 weeks after infection. Approximately 15% to 35% of persons who acquire HCV are able to clear the infection spontaneously. The remaining 55% to 85% develop chronic infection. Spontaneous resolution is more common among infected women and infants.

Among patients with chronic HCV infection, 5% to 25% will develop cirrhosis over a period of 20 to 30 years. Risk factors for disease progression include male sex, age greater than 40 years at the time of infection, co-infection with HIV or hepatitis B, and daily alcohol use of more than 50 g (about 3 drinks) per day. Among patients with cirrhosis, the risk for hepatocellular carcinoma is 1% to 3% per year. An estimated 1% to 5% of HCV-infected patients will die as a consequence of some complication related to their infection (liver disease or cancer).

Each year, HCV infection accounts for approximately 8,000 to 10,000 deaths in the United States. In addition to liver disease, 10% to 40% of patients with HCV infection develop at least 1 extrahepatic disease manifestation. These comorbidities include arthralgia, cutaneous manifestations, xerostomia, xerophthalmia, sensory neuropathy, and cryoglobulinemia. In its most severe form, cryoglobulinemia may present with systemic vasculitis and glomerulonephritis. Furthermore, an association between HCV infection and an increased risk for insulin resistance and type 2 diabetes recently has been identified.

There are 6 major genotypes of HCV. In the United States, approximately 72% of HCV-infected patients have genotype 1 and 16% to 19% have genotype 2. It is possible for a person who has become infected with one HCV genotype of HCV to become re-infected with another.

### Diagnosis and Evaluation

The United States Preventive Services Task Force recommends against routine screening for HCV infection. Table 1 lists the persons for whom HCV screening is recommended.

The screening test of choice for identifying HCV infection is an enzyme immunoassay for HCV antibodies. The specificity of this test is about 99%. False-positives do occur, especially when the test is applied in a low-risk population, such as healthy blood donors. False-positives also may occur in patients with certain autoimmune diseases and hypergammaglobulinemia. Conversely, false-negatives may be seen in patients with immunodeficiency disorders, hypogammaglobulinemia, or immediately following HCV exposure and prior to the development of antibodies.

A positive HCV antibody test warrants confirmatory testing, usually through PCR testing.
for the presence of HCV RNA. If the result is confirmed, quantitation of viral load and genotyping should take place.\textsuperscript{3,5,12} Both provide useful information for prognostication and diagnostic decision making. Response to treatment is significantly higher in patients infected with genotype 2 HCV (70% to 80%) than for those with genotype 1 HCV infection (40% to 50%).\textsuperscript{3,8,10}

The role of liver biopsy in the assessment of patients with HCV infection is controversial.\textsuperscript{3,5} Liver biopsy is the gold standard for determining the degree of liver fibrosis. However, the procedure is not without risk; an estimated 1% to 5% people who undergo liver biopsy require hospitalization. Therefore, some practitioners argue against its routine use.\textsuperscript{10} The results of liver biopsy are especially helpful when weighing the risks and benefits of treatment in patients with HCV infection and significant comorbid diseases. Alternative noninvasive techniques by which to grade the extent of liver fibrosis such as transient elastography are in development but are not in widespread use.\textsuperscript{3}

**Treatment**

HCV infection has no cure, but certain therapies have been shown to significantly reduce the progression of liver disease. The current treatment of choice is pegylated interferon-\(\alpha\) (PEG/IFN-\(\alpha\)) plus ribavirin. The recommended duration of therapy is 24 weeks for patients with HCV genotypes 2 and 3 and 48 weeks for patients with HCV genotypes 1 and 4.\textsuperscript{3} Treatment should be considered for all HCV patients who are at least aged 18 years and are willing to comply with therapy.\textsuperscript{3} Therapy is widely accepted for HCV-positive patients with abnormal AST/ALT levels and/or evidence of liver fibrosis on biopsy. Treatment also may be considered for patients with either no or mild liver fibrosis, normal AST/ALT levels, and for those who have failed prior treatment with IFN or PEG/IFN only.

In patients taking IFNS, flu-like symptoms are common, especially early in the course of treatment.\textsuperscript{3,15} Psychiatric disorders including depression, confusion, and irritability occur in 30% of patients on IFN therapy.\textsuperscript{1} Anemia, leukopenia, and thrombocytopenia are reported in as many as 50% of patients.\textsuperscript{3,12,15} IFN also may induce or exacerbate autoimmune conditions, such as thyroiditis or hepatitis.\textsuperscript{3}

Ribavirin therapy is associated with hemolytic anemia, pruritus, nasal congestion, and elevated uric acid levels.\textsuperscript{15} Ribavirin is cleared renally; therefore, dose adjustments are required when given to patients with preexisting renal disease. Ribavirin also is teratogenic in animals.\textsuperscript{15}

For some patients, the side effects of HCV treatment outweigh its benefits. Treatment is generally contraindicated in patients with significant concurrent heart, kidney, or lung disease, uncontrolled depression, untreated thyroid disease, or autoimmune hepatitis. Therapy is not recommended for recipients of solid organ transplants, pregnant women, women who refuse contraceptive therapy, and children under the age of 2 years.\textsuperscript{3,5}

The best predictor of long-term treatment efficacy is a sustained virologic response (SVR), defined as the absence of HCV RNA by PCR assay 24 weeks following cessation of treatment.\textsuperscript{3} In addition to viral genotype, certain other factors are associated with a lower probability of treatment response and include high pretreatment viral load, black race, age greater than 40 years, male sex, BMI greater than 25 kg/m\(^2\), and greater degree of liver fibrosis at the initiation of treatment.\textsuperscript{1,3,10}

Approximately 30% of patients treated with PEG/IFN-\(\alpha\) and ribavirin do not achieve a virologic response. Another group of patients experience virologic relapse, which usually occurs within the first 12 weeks of treatment. In non-responders, retreatment with the same regimen is rarely effective and
therefore not recommended. Recent trials suggest that some of these patients may achieve an SVR using a combination of direct-acting antiviral agents such as asunaprevir and daclatasvir with or without PEG/IFN and ribavirin. For patients who relapse, retreatment with PEG/IFN-α and ribavirin may be considered, particularly for those with significant liver fibrosis or cirrhosis.

**Anesthetic Considerations**

Elective surgery is not advisable in patients with acute hepatitis of any kind because of increased perioperative morbidity and mortality. For patients with stable chronic HCV infection, general principles of care include attention to preexisting liver insufficiency and avoidance of drugs, such as acetaminophen, isoniazid, methyldopa, and phenytoin. Laboratory assessment should include measurement of serum chemistries, AST/ALT levels, bilirubins, complete blood count, and coagulation profile. Serum albumin also is useful in patients with moderate to severe fibrosis or cirrhosis. Signs and symptoms of asterixis, ascites, and gastroesophageal varices should be sought. The Model for End-Stage Liver Disease (MELD) score is used to estimate the probability of survival in patients with liver disease based on 3 variables: INR; serum creatinine; and total bilirubin. It is the scoring system used by the United Network for Organ Sharing to prioritize patients on the waiting list for liver transplant and to predict survival after transplantation. It also is useful in estimating preoperative risk (Table 2).

<table>
<thead>
<tr>
<th>Score</th>
<th>3-Mo Mortality, %</th>
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<tr>
<td>≥40</td>
<td>71.3</td>
</tr>
<tr>
<td>30-39</td>
<td>52.6</td>
</tr>
<tr>
<td>20-29</td>
<td>19.6</td>
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<td>10-19</td>
<td>6.0</td>
</tr>
<tr>
<td>0-9</td>
<td>1.9</td>
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</tbody>
</table>

Table 2. Calculation of the MELD Score

\[ \text{MELD Score}^a = 10(0.957 \ln(\text{Scr}) + 0.378 \ln(\text{Tbil}) + 1.12 \ln(\text{INR}) + 0.643) \]

\[ \text{INR, international normalized ratio; MELD, Model for End-Stage Liver Disease; Scr, serum creatinine; Tbil, total bilirubin} \]

\[ ^a \text{If the patient has been dialyzed within the last 7 d, use 4.0 as the serum creatinine value.} \]
\[ ^b \text{Any value <1 should be rounded to 1} \]

Adapted from reference 18

There is no preferred anesthetic technique for patients with chronic HCV infection. Drug pharmacokinetics may be altered as a result of end-organ dysfunction, reduced serum proteins, high cardiac output, or altered liver perfusion. Regional anesthesia is appropriate if the platelet count and coagulation profile are within normal limits. There is no evidence that HCV is found in appreciable quantities in cerebrospinal fluid or causes damage to the central nervous system.

Patients with liver disease tend to have a hyperdynamic circulation, marked by increased cardiac output and low systemic vascular resistance. Splanchnic vasodilation contributes to the formation of ascites and reduced effective circulating volume. Vasopressors may be required in the context of anesthetic induction or with the use of volatile agents. The goal of fluid management in these patients is to maintain adequate organ perfusion. Vasopressin and vasopressin analogues may be particularly useful, as they have been shown to increase splanchnic resistance and improve renal blood flow and glomerular filtration rate.

Invasive hemodynamic monitoring may facilitate the management of these patients. Patients with cirrhosis are at increased risk for infection. Therefore, the timely administration of pre-incision antibiotics and close attention to sterile technique are crucial.
Narcotics are appropriate for postoperative pain control; however, dosage should be carefully titrated. Acetaminophen and nonsteroidal anti-inflammatory drugs should not be administered to patients with advanced liver disease, although they may be used in patients with mild liver dysfunction in normal doses.

**Nosocomial Transmission**

Nosocomial transmission of HCV infection has been documented to occur only through contact with blood, blood products, or bodily fluids containing blood.\(^3\) The odds of transmission of HCV infection from an HCV-infected needlestick or sharps injury are approximately 1% to 2% per incident.\(^1,8,9,19\) Over a career, it has been estimated that the lifetime HCV seroconversion risk for a surgeon may be as high as 5%\(^20\).

Following any exposure, an employee should report to occupational health or the emergency department as soon as possible. The wound should be thoroughly washed with antimicrobial solution. Current guidelines recommend monitoring for HCV antibody seroconversion at 3 and 6 months. Initiation of HCV drug treatment is not recommended unless seroconversion occurs.\(^15\)

Patient-to-patient transmission of HCV has been known to occur through the improper use of multidose vials in which used syringes or needles resulted in drug contamination.\(^21-26\) Reusable parts of a breathing apparatus also have been implicated, probably also as a result of occult blood contamination.\(^27\) A study conducted in the Netherlands showed that one-third of operating room surfaces had evidence of occult blood contamination. These areas included laryngoscope blades, pulse oximeters, and other reusable medical equipment.\(^28\) The use of IV tubing with 1-way valves to prevent blood contact and transition to single-use medical devices aid in the prevention of nosocomial HCV transmission.

Although rare, there also are reports of anesthetist-to-patient transmission of HCV.\(^29-32\) In some cases, no obvious breaches of standard precautions were identified. The most likely source of infection is thought to be contact with exposed skin lacerations. The practice of introducing a finger into the patient’s mouth during intubation may be a source of exposure for the patient. Even if gloves are worn, undetected perforations may be present.\(^32\)

No recommendations call for restricting the professional activities of HCV-positive health care workers.\(^8,9\)

In all cases, standard precautions and strict adherence to aseptic technique are paramount. It has been estimated that the risk for HCV transmission from an infected surgeon to a patient would occur in approximately 1 in 10,000 cases; the risk would be expected to be lower for anesthesiologists, given that they perform less exposure-prone procedures.\(^33\)

**Management of the Case Presented**

Given the absence of acute liver dysfunction, the decision was made to proceed with the case. On the day of the surgery, an epidural catheter was inserted prior to induction of general anesthesia. While cleaning up sharps after completion of the procedure, the anesthesia resident stuck her finger with the contaminated epidural needle. Permission was obtained from the patient’s wife to perform a full hepatitis panel and testing for HIV. Aside from HCV, no other infection was identified.
HCV antibody and liver enzymes were performed on the anesthesia resident at the time of the event and at 3 and 6 months thereafter.\textsuperscript{15} She remained HCV antibody–negative and no treatment was recommended.

**Concluding Statement**

HCV infection is an often asymptomatic but potentially fatal disease. Although progression of the illness usually can be slowed, there is no cure. Due to exposure to blood in the operating room, hepatitis C poses a work-related risk for anesthesiologists. Extreme care must be taken to avoid needlestick contamination, especially from patients identified as high risk for hepatitis infection.

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REFERENCES


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**Post-test**

1. The prevalence of HCV infection in the adult population of the United States is approximately
   a. 1.3%
   b. 4.1%
   c. 8.9%
   d. 13.9%

2. The risk for neonatal transmission of HCV from an infected mother is
   a. <10%
   b. 10%-20%
   c. 25%-35%
   d. 50%-60%

3. The pharmacologic treatment regimen of choice for patients with HCV infection is .
   a. Ribavirin and asunaprevir
   b. Hepatitis C immunoglobulin
   c. Pegylated interferon-α only
   d. Pegylated interferon-α plus ribavirin

4. The risk for transmission of HCV from a needlestick injury involving a known hepatitis C-positive patient is approximately
   a. 1%-5%
   b. 5%-10%
   c. 10%-15%
   d. 15%-20%

5. Following acute infection, when are antibodies to HCV most likely to appear in the blood?
   a. 1-4 wk
   b. 4-8 wk
   c. 8-12 wk
   d. 12-16 wk
6. What is the most common HCV genotype in the United States?
   
   a. 1 
   b. 2 
   c. 3 
   d. 4 

7. What HCV genotype is most responsive to pharmacologic treatment?
   
   a. 1 
   b. 2 
   c. 3 
   d. 4 

8. Which of the following patient characteristics is associated with a favorable response to pharmacologic HCV treatment?
   
   a. Black race 
   b. Body mass index >25 kg/m2 
   c. Male gender 
   d. Age <40 y 

9. What percentage of people with HCV will develop cirrhosis in the decades following infection?
   
   a. 5%-10% 
   b. 15%-25% 
   c. 25%-40% 
   d. 60%-70% 

10. In what percentage of people is acute HCV infection asymptomatic?
    
    a. 10%-20% 
    b. 30%-40% 
    c. 60%-70% 
    d. 80%-90%