Key Principles

- Approximately 3% of the world’s population is infected with the hepatitis C virus (HCV) with the highest prevalence rates noted in Africa and Asia.
- In the United States, the incidence of HCV infection is declining secondary to effective blood donor screening adopted in the early 1990s and changing practices of intravenous drug users due to an increased awareness of HIV and hepatitis.
- Hepatitis C can be categorized into six genotypes and 50+ subtypes. Genotypes 1a and 1b are the most common, accounting for about 60% of global infections.
Hepatitis C is transmitted primarily via parenteral routes. Mucosal exposures to blood or serum-derived fluids and environmental sources also play a role in HCV transmission.

Controversy exists regarding the natural history of hepatitis C. While many experts view hepatitis C as a progressive disease with a high likelihood of advancing to cirrhosis, hepatocellular carcinoma, and death, others consider this virus to be more variable in nature, with the majority of patients “dying with the disease, not of the disease.” The CDC estimates that up to 20% of chronic HCV infections lead to cirrhosis over a period of 20–30 years.

Several factors influence the rate of progression of hepatitis C. Progression is hastened when acquired via blood transfusion; at an older age; in males; in non-African-Americans; in the setting of excessive alcohol (and possibly tobacco) use; and, in persons with HIV and/or HBV coinfection or features of metabolic syndrome. It is controversial if HCV viral load and genotype affect the evolution of disease.

1. EPIDEMIOLOGY

1.1. Global Prevalence and Incidence

The World Health Organization (WHO) reports that approximately 3% of the world population, or 170 million persons, is infected with the hepatitis C virus (HCV) with between 3 and 4 millions new infections each year (1). Limitations of global HCV epidemiological data include lack of data submission from numerous countries, variations in the population groups studied, and differing methods of data collection and interpretation. The majority of studies extrapolate data from blood donors alone, which is not representative of the entire population and is likely an underestimate.

Figure 1 illustrates the global prevalence of HCV. Africa and Asia have the highest reported prevalence rates, in contrast to the low rates of HCV in North America, Western Europe, and Australia. Egypt has an unusually high prevalence of hepatitis C even by the standards of other developing nations with 20% of Egyptian blood donors positive for HCV antibody. Previous parenteral therapy for Schistosomiasis with inadequate sterilization techniques has been implicated as the cause for this high prevalence rate (2). Similar epidemiological events explain other countries’ spike in infection rates. For example, Italy’s HCV prevalence rate of 12.6% is attributed to the improper use of glass
syringes for administration of the Salk vaccine to prevent polio in the 1960s (3). Japan’s prevalence rate of 2.6% is thought to be secondary to the use of injection methamphetamines in the 1950s (WHO).

1.2. United States Prevalence and Incidence

HCV is the most common bloodborne infection in the United States. The estimated prevalence of HCV seropositivity in the United States general population is 1.6% or 4.1 million persons. Of those who are anti-HCV positive, 79.7%, or 3.2 million persons, have chronic infection. The prevalence is highest among non-Hispanic black males between 40 and 49 years of age. This data is derived from the most recent National Center for Health Statistics (NHANES) survey (1999–2002) of 15,079 random participants whose serum samples were tested for HCV antibody and HCV RNA (4). This information is consistent with results from NHANES III (1988–1994), except that peak prevalence data have shifted from ages 30–49 to 40–49 (representing similar birth-year cohorts) (5). Figure 2 illustrates this data.

A drawback to analyzing the NHANES population is the exclusion of incarcerated, institutionalized, and homeless persons. The Centers for Disease Control (CDC) estimates that if the incarcerated population is included, 3.5 million persons have chronic HCV infection (6). Cheung et al. (7) performed a retrospective analysis of homeless veterans admitted to a domiciliary facility at the VA Palo Alto Health Care
Fig. 2. Prevalence of anti-HCV in the United States, 1999–2002.

System and found a 41.7% prevalence of HCV seropositivity, suggesting that homeless persons represent a significant pool of chronic HCV infection.

Studies focusing on specific populations have shown varying prevalence rates. For example, Dominitz et al. (8) reported a prevalence rate of 4.0% among a Department of Veteran Affairs (VA) patient population randomly selected from 20 VA centers. This is lower than prior estimates that have ranged from 6.6 to 35% (9–11). Among 10,000 active duty military personnel, Hyams et al. (12) found an overall HCV seropositivity prevalence rate of 0.48%; this rate was lower (0.1%) in persons aged lesser than 30 as compared to those aged greater than 40 (3.0%). The lower prevalence among active duty members compared to the general VA population can be attributed to mandatory illicit drug testing throughout military service since 1971. Recently, Tabibian et al. (13) reported a seropositivity prevalence of 38% among 129 veterans in a psychiatric ward. Among health-care workers at Johns Hopkins Hospital, a prevalence of 0.7% was reported, comparable to that observed in local blood donors (14).

In the United States, the incidence of HCV infection is declining secondary to effective blood donor screening adopted in the early 1990s and changing practices of intravenous drug users due to an increased
awareness of HIV and hepatitis. This decline is illustrated in Fig. 3 (15). The CDC estimates that while there were 180,000 new cases per year in the 1980s, this declined to 20,000 new cases in 2005 (15). This data is based on cases reported voluntarily to the CDC by state and territorial health departments via the National Electronic Telecommunications System for Surveillance (NETSS). Figure 3 illustrates the declining incidence of acute hepatitis C.

1.3. Genotype

Hepatitis C can be categorized into six genotypes and 50+ subtypes. It is important to note an infected person’s specific genotype as it affects treatment dose, duration, and response. NHANES III reported that 73.7% of the US population is infected with genotype 1 (5).

Genotypes 1–3 have a worldwide distribution. Genotypes 1a and 1b are the most common, accounting for about 60% of global infections. They predominate in Northern, Southern, and Eastern Europe; North America; and Japan. Genotype 2 is less frequently represented than genotype 1 and is often associated with the risk factor of prior blood transfusion (16). Type 3 is common in Southeast Asia and is variably distributed in different countries. In Western countries, it is often associated with a history of illicit drug use (16, 17). Genotype 4 is principally
found in the Middle East, Egypt, North and Central Africa. Type 5 is found almost exclusively in South Africa, and genotype 6 is distributed throughout Asia (39, 58, 94, 103) (Table 1).

### 2. RISK FACTORS

Hepatitis C is transmitted primarily via parenteral routes. Mucosal exposures to blood or serum-derived fluids and environmental sources also play a role in HCV transmission. Currently the predominant risk factor for HCV in the United States is intravenous drug use. Prior to 1990, blood transfusions contributed the majority of cases; however, with the adoption of effective blood donor screening programs and eventually universal serological screening, this method of transmission has been virtually eliminated. According to a large case–control study of US blood donors, injection drug use, history of blood transfusion, and sex with an injection drug user are the three commonest risk factors for HCV, whereas drug inhalation and high-risk sexual activity are not independently associated with hepatitis C (18). NHANES III reported an association between HCV and marijuana and/or cocaine use, in addition to high-risk sexual behavior (5). Dominitz et al. conducted a study involving veterans with hepatitis C at 20 Veteran Affairs medical centers and found that 78% reported intravenous drug use or blood transfusion as a risk factor. Among patients with HCV infection, 20–40% of patients do not have an identified risk factor for transmission. Karmochkine et al. surveyed 450 HCV patients without a history
of intravenous drug use or blood transfusion and 757 anti-HCV-negative controls. Multivariate analysis illustrated 15 independent risk factors for transmission including gastrointestinal endoscopy, intravenous or intramuscular injections, varicose vein sclerotherapy, acupuncture, contact sports, beauty treatments, and intranasal cocaine use (19). Kamili et al. conducted an experimental study that showed that HCV in blood is infectious even after exposure to drying and storage at room temperature (20). This study supports the notion that environmental sources are a potential route for HCV transmission.

In 1998, the CDC recommended routine screening in persons at high risk for HCV infection (21). This recommendation was also endorsed by the National Institutes of Health (22) and Veterans Administration (VA) (23). In 2004, the US Preventive Services Task Force (USPSTF) recommended against screening for HCV in the general population and found insufficient evidence to advocate HCV screening of high-risk patients (24). Drs. Alter, Seeff and colleagues responded to the USPSTF recommendations by stating that HCV screening for high-risk patients is necessary to provide infected persons with counseling and potential treatment (25). Mallette et al. studied the clinical characteristics and outcomes of HCV patients diagnosed via a screening program based on risk factors. Results showed that 7.3% of patients who underwent screening were anti-HCV positive and 4.3% were viremic. Of the patients who tested positive for anti-HCV, 47% were considered treatment candidates. This study supports a policy of HCV screening for persons with identified risk factors to provide appropriate counseling and identify candidates for hepatitis A and B vaccination as well as antiviral therapy (Table 2 and Fig. 4).

Fig. 4. Risk factors for HCV.
### Table 2

**CDC Recommendations for HCV screening**

<table>
<thead>
<tr>
<th>Testing recommended</th>
<th>Uncertain need for testing</th>
<th>Testing not recommended</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current and former injection drug users</td>
<td>Recipients of transplanted tissue</td>
<td>Health care workers</td>
</tr>
<tr>
<td>Recipients of clotting factors before 1987</td>
<td>Intranasal cocaine users</td>
<td>Pregnant women</td>
</tr>
<tr>
<td>Hemodialysis patients</td>
<td>Persons with tattoos</td>
<td>Household contacts</td>
</tr>
<tr>
<td>Recipients of blood and/or solid organs before 1992</td>
<td>Persons with body piercings</td>
<td>General population</td>
</tr>
<tr>
<td>Persons with undiagnosed liver test abnormalities</td>
<td>Persons with multiple sexual partners/STDs</td>
<td></td>
</tr>
<tr>
<td>Infants born to infected mothers after 12–18 months</td>
<td>Long-term monogamous relationship with person infected with HCV</td>
<td></td>
</tr>
<tr>
<td>Health care/public safety workers with a known exposure</td>
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### 2.1. Intravenous Drug Use

Currently, the majority of cases of HCV transmission can be attributed to intravenous drug use through the sharing of needles, syringes, and other paraphernalia (26–28). The CDC estimates that intravenous drug use accounts for up to 60% of new cases of HCV. The annual incidence of HCV transmission among intravenous drug users ranges from 15 to over 30% (29). Furthermore, the CDC reports that 60–80% of persons who have used intravenous drugs for 5 or more years are infected. Villano et al. conducted a prospective study of active intravenous drug users from Baltimore, MD and found that 30.3% participants became anti-HCV positive, mostly within the first 2 years of surveillance (30). Similarly, the Hepatitis C European Network for
Cooperative Research (HENCORE) group reported an 80% prevalence rate among intravenous drug users (31).

### 2.2. Blood Products

The CDC reports that prior to 1989, blood transfusions were associated with a 7–10% risk of HCV transmission. As a result of the routine implementation of sensitive anti-HCV serological testing in 1992, the risk of hepatitis C acquisition via blood transfusion is currently 0.001% per unit transfused (32) as compared to 0.02% per unit transfused prior to effective blood donor screening (33). This minimal risk is attributed to the potential for transmission during the window period of infection, which occurs after transmission, but prior to detectable HCV antibody. The introduction of nucleic acid testing will further reduce this risk (34, 35). There have been no transfusion-associated HCV cases in the United States since 1992 among an NIH blood recipient population (28, 36). Although transfusion-associated HCV has declined in the United States, the incidence still remains high in certain parts of the world. In a recent study, 147 Chilean patients with chronic HCV were interviewed and blood transfusion was found to be the most common risk factor associated with infection: 54% of HCV-infected persons gave a history of blood transfusion, while only 5% had a history of intravenous drug users (37).

Prior to the implementation of procedures to inactivate viruses from pooled plasma in 1987, persons who received clotting factor concentrates were at high risk of HCV transmission. In fact, prevalence rates in the setting of hemophilia were as high as 90% (38, 39). An outbreak of HCV occurred among recipients of intravenous immune globulin that was not inactivated for viruses in 1993 (40, 41). Although administration of intramuscular immune globulin has not been implicated as a risk factor for HCV transmission, inactivation of viruses is now required for both intravenous and intramuscular immune globulin in the United States (21). Two large outbreaks of HCV were linked to contaminated anti-rhesus D preparations given to female recipients during childbirth (42, 43).

### 2.3. High-Risk Sexual Activity

Several case reports and studies have provided evidence that sexual activity is independently associated with transmission of HCV (44–47). Rates of transmission of hepatitis C are lower than those of hepatitis B and HIV (48, 49). CDC surveillance data in 2005 indicated that 15–20% of persons with acute HCV infection reported a history of sexual exposure as the only identifiable risk factor. Persons with a history
of sexually transmitted diseases, multiple sexual partners, vigorous sexual practices, and male homosexual activity are at greatest risk of HCV acquisition. Among heterosexuals, male to female transmission is more efficient than female to male transmission (50). On the contrary, several case–control studies did not find a link between acquisition of hepatitis C and either homosexual activity (44, 45, 51) or sexual promiscuity (51, 52). In the NHANES III study, the number of sexual partners and age of first sexual intercourse correlated with HCV seroconversion. Thomas et al. studied 1257 persons who denied intravenous drug use at an STD clinic in Baltimore, MD, and found that 9.7% were positive for anti-HCV (53). Alter postulated that HCV is more likely to be transmitted via sexual intercourse in the setting of acute infection, high viral load, and a lack of antibody to complex with antigen (26). Several studies have found an increased risk of HCV transmission among heterosexual partners in the setting of coinfection with HIV (49, 54). Terrault reports that among high-risk individuals with hepatitis C, there is a 1% annual risk of HCV transmission (50) (Table 3).

2.4. Intrafamilial and Monogamous Sexual Transmission

Intrafamilial transmission of hepatitis C has been reported (55). Oshita et al. performed a study of 219 family members including spouses, children, and others who lived with 99 HCV-infected individuals. These family members were tested for ALT, anti-HCV +/- HCV RNA PCR and compared to a control population with similar demographic characteristics. Results showed that 26 family members (12%) tested positive for anti-HCV, specifically 18/75 (24%) spouses, 5/110 (5%) children, and 3/34 (9%) others, compared to 6 (2%) persons in the control group. These rates were similar to previous studies (56, 57). Of the family members with HCV seropositivity, 81% were HCV RNA positive. The higher rate of HCV seropositivity among spouses could have been secondary to sexual transmission. The rate of anti-HCV positivity increased with age and decades of marriage (55). More recently, a systematic review was performed to examine the risk of HCV transmission between infected patients and household contacts and stable heterosexual partners. The prevalence of HCV seropositivity among 4250 stable sexual contacts of patients with hepatitis C was 13.48%. Of 580 sexual contacts of patients who had acquired HCV via blood transfusions, the rate of HCV seropositivity was lower at 2.41%. Among household contacts, there was a 4.0% risk of transmission compared to 0% in contacts of anti-HCV-negative controls (58). Diago et al. reported an overall 4.5% prevalence of anti-HCV among household contacts with 30/394 (7.6%) of heterosexual stable partners and 35/1057 (3.3%)
### Table 3

Reported Rates of Chronicity of HCV Infection

<table>
<thead>
<tr>
<th>Study</th>
<th>Patient population</th>
<th>Mode of transmission</th>
<th>% Chronic infection</th>
</tr>
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<tbody>
<tr>
<td>Thomas et al., 2000 (93)</td>
<td>919 persons with a history of intravenous drug use</td>
<td>Intravenous drug use</td>
<td>90</td>
</tr>
<tr>
<td>Alter HJ, 1997 (28)</td>
<td>248 asymptomatic blood donors</td>
<td>Blood transfusion, intranasal drug use, intravenous drug use (50%), sexual contact, male ear piercing</td>
<td>86</td>
</tr>
<tr>
<td>Villano et al., 1999 (94)</td>
<td>43 persons with acute HCV</td>
<td>Intravenous drug use</td>
<td>86</td>
</tr>
<tr>
<td>Seeff et al., 2001 (96)</td>
<td>90 blood recipients</td>
<td>Blood transfusion</td>
<td>77</td>
</tr>
<tr>
<td>Seeff et al., 2000 (95)</td>
<td>17 military recruits with stored blood samples from 1948–1954</td>
<td>Unknown</td>
<td>65</td>
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<td>62</td>
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</table>

of nonsexual contacts affected. Although the prevalence of anti-HCV among children of HCV-infected individuals was lower than other household contacts, the risk was higher when the mother was the index case (3%) as compared to the father (0.6%). Again, an increased prevalence was seen with increasing age (59). Saliva has also been cited as a possible route of HCV transmission (60, 61).
On the other hand, Caporaso et al. reported that after adjustment for confounders, sexual transmission does not play a role in intrafamilial spread of HCV infection (62). In addition, Stroffolini et al. found HCV transmission between spouses is likely secondary to parenteral exposures, and less likely sexual transmission (63). Kao et al. performed a prospective study of 112 anti-HCV-positive patients and their anti-HCV-negative spouses. There was one seroconversion occurrence at 2 years over a follow-up period of 45.9 months. The annual interspousal transmission of HCV was 0.23%, with the possibility of a cumulative risk (64). Vandelli et al. reported the results of a prospective study in which 7879 HCV-infected persons and their anti-HCV-negative spouses were followed for 10 years. Three HCV seroconversions were observed for an incidence rate of 0.37 per 1000 person-years (65). Terrault reports a 0–0.6% annual risk of transmission and a 2.7% prevalence rate among monogamous partners of patients with hepatitis C (49). The National Institutes of Diabetes and Digestive and Kidney Diseases (NIDDK) reports an annual transmission rate of <1% per year and does not recommend a change in sexual practices among monogamous couples.

Tahan et al. were the first to quantify HCV seroconversions in anti-HCV-negative spouses of HCV-infected persons in terms of sexual encounters. Six hundred persons with spouses who were anti-HCV positive were tested for anti-HCV. Twelve (2%) persons were anti-HCV positive and 11 were HCV-RNA positive. Persons positive for anti-HCV engaged in a greater number of sexual encounters (434 ± 295 vs. 307 ± 333). This population was followed prospectively for 3 years. There was no evidence of new seroconversion for 3 years and 257.9 ± 72.2 sexual occurrences (66).

Collectively, this data suggests that both household contacts and sexual partners may be at increased risk – albeit small – of transmission of hepatitis C, with sexual contacts being at higher risk. Terrault advocates that family members should not share items that may be contaminated by blood (50).

### 2.5. Mother to Infant Transmission

Vertical transmission is a known risk factor for HCV infection. Coinfection with HIV and increased viremia are thought to contribute to an even greater risk. Ferrero et al. prospectively studied 170 anti-HCV-positive women and their 188 newborn babies to determine the rate of vertical transmission. Babies were followed until clearance of anti-HCV or diagnosis of HCV infection. Results revealed a 2.0% rate of HCV transmission among HIV-negative women, which increased to 5.4% with HIV coinfection. Increased maternal viremia was associ-
ated with an increased risk of transmission. With regard to clearance of anti-HCV among noninfected infants, babies born to viremic mothers have a slower rate of clearance of anti-HCV as compared to nonviremic mothers (67). Another prospective study of 86 infants born to anti-HCV-positive mothers showed similar results and also reported that HCV transmission is not affected by mother’s age, route of delivery, or genotype, but may be increased in the setting of active intravenous drug use and HCV/HIV coinfection (68). Hunt et al. reviewed studies from 1988 through 1996 and suggested that rates of vertical transmission may be higher among mothers with acute HCV infection as compared to chronic HCV infection (69). Although most studies do support an increased risk of mother to child transmission of HCV in the setting of HIV coinfection, Manzini et al. reported slower clearance of passively acquired anti-HCV among HIV-positive mothers, without an increase in vertical transmission of HCV (70). Airoldi has suggested that highly active antiretroviral therapy may significantly decrease the risk of vertical transmission of HCV (71).

2.6. Breastfeeding

Several studies (69, 72, 73) and the CDC report no evidence linking HCV transmission to breastfeeding; therefore, HCV infection is not a contraindication to breastfeeding. However, if a mother’s nipples are cracked and bleeding, she should temporarily refrain from breastfeeding as a precautionary measure (72). Kumar performed a prospective study of 65 HCV-RNA-positive women and 42 anti-HCV-negative controls to assess breastfeeding as a mode of HCV transmission. All infants studied were breastfed. Five mothers with chronic HCV developed symptomatic liver disease and three of their infants were found to be HCV-RNA positive during a 12-month follow-up period. The authors concluded that women with symptomatic chronic HCV and high viral loads should not breastfeed (74). In the setting of HCV/HIV coinfection, breastfeeding is discouraged (71).

2.7. Hemodialysis

Although hemodialysis is a well-known risk factor for HBV transmission, the CDC only recently cited it as a risk factor for HCV transmission. Recommendations for the prevention of hepatitis B in hemodialysis centers were initially published in 1977, with implementation of vaccination among patients and staff since 1982. These strategies led to a sharp decline in HBV transmission.

With regard to HCV, limited data from US studies since 1990 have reported a 3% annual incidence of HCV transmission in the setting of
hemodialysis without a history of intravenous drug use or blood transfusions (75, 76). In 1999, the national prevalence rate of anti-HCV was 8.9%, with a greater than 40% rate among some hemodialysis centers (unpublished CDC data, 2001) (77). Higher rates of anti-HCV seroconversion were seen among persons on hemodialysis for 5 years or more, with rates increasing from 12% among persons on hemodialysis for less than 5 years to 37% among persons on hemodialysis for 5 or more years (75, 78, 79). During 1999–2000, the CDC studied three HCV outbreaks in hemodialysis centers and found that transmission occurred because of inadequate infection control practices. Seroconversion was associated with patients receiving hemodialysis immediately following a patient with chronic HCV, use of equipment and supplies that were not disinfected between patient use, shared utilization of medication carts and medication vials, and blood spills that were not promptly cleaned.

In 2001, the CDC recommended the implementation of infection control practices specific to hemodialysis units, infection control training and education, and routine surveillance of hepatitis C for hemodialysis patients. Monthly ALT assessment and biannual anti-HCV antibody testing were suggested as initial testing modalities, with HCV PCR reserved for those with elevated transaminases of unknown etiology. Anti-HCV testing was not recommended for hemodialysis staff members. In addition, isolation of patients with hepatitis C was not considered necessary (77).

The above recommendations resulted in an increase in the number of hemodialysis centers testing for HCV from 56 in 1999 to 64% in 2002. The prevalence rate of HCV decreased from 8.9 in 1999 to 7.8% in 2002. This decline in prevalence was attributed to a decline in new infections due to an increased awareness of HCV transmission in hemodialysis settings. In April 2008, the Kidney Diseases Improving Global Outcomes Foundation developed the first international clinical practice guidelines to address the prevention of hepatitis C in patients undergoing hemodialysis. Although several nephrology organizations recommend mandatory semiannual testing of anti-HCV in hemodialysis patients, the Centers for Medicare and Medicaid Services (CMS) do not reimburse providers for the cost of this testing unless there is a suspicion that the patient has been exposed to HCV-infected blood (80).

### 2.8. Intranasal Drug Use

Although several studies have reported that intranasal drug use is not independently associated with an increased risk of HCV transmission (81, 82), others have noted an association (28). The CDC has described it as a potential risk factor, primarily through sharing of pipes and
straws. The National Institutes of Diabetes and Digestive and Kidney Diseases (NIDDK) states that intranasal cocaine use is associated with a *slightly* increased risk of hepatitis C. McMahon et al. reviewed the epidemiological evidence of HCV transmission in the setting of oral and intranasal drug use and found that although current studies do not dismiss these modes of transmission, further research is needed (83).

### 2.9. Tattoos

The concept of tattooing as an independent risk factor for HCV transmission is controversial with various studies relaying discordant results. Ko et al. studied 213 healthy young men who denied participation in intravenous drug use or high-risk sexual activity. Results revealed that 11/187 (12.6%) men with tattoos as opposed to 3/126 (2.4%) tattoo-free men were positive for anti-HCV. The risk of HCV seropositivity was higher with an increased number of tattoos and non-professional status of the tattooer (84). Hellard et al. conducted a survey and found tattooing during incarceration to be an independent risk factor for HCV transmission among a group of prisoners in Australian correctional facilities (85). Neumeister et al. studied the risk factors and prevalence of HCV among native Americans and found tattoos > 5 years old to be a strong risk factor for transmission (86). Haley et al. reported a higher risk of HCV acquisition with commercial tattooing as compared to intravenous drug use (87). Haley also postulated that tattooing may be associated with subclinical HCV infection, while intravenous drug use may lead to an acute infection (88). The CDC acknowledges that although several studies have found an association between tattooing and HCV transmission in select populations, they may not pertain to the general population. As less than 1% of persons with hepatitis C reported a history of tattooing in the CDC’s surveillance system, the CDC believes that further studies are needed to determine if tattooing is a risk factor for HCV transmission.

### 2.10. Health Care Setting

Hauri et al. reported that up to 40% of worldwide HCV infections can be attributed to contaminated health care injections in developing countries (89). Contaminated glass syringes for Schistosomiasis treatment have been implicated as a mode of HCV transmission in Egypt (2), while multiple injections for kala-azar treatment have been associated with HCV seropositivity in India (90). The World Health Organization has found the highest rates of therapeutic needle reuse in Southeast Asia, Middle East, and the Western Pacific. In order to combat unsafe therapeutic injection practices, the WHO implemented the
Safe Injection Global Network (SIGN), a partnership of various governments, international health agencies, and corporations that advocate safer worldwide injection practices (27).

Regarding occupational transmission of HCV, health-care workers exposed to hollow-bore or deep tissue needle stick injuries from an HCV-positive source have a 1.8% risk of transmission, which is lower than that of HBV and HIV (26, 91). The prevalence of HCV infection among health-care workers is similar to the general population (26).

3. NATURAL HISTORY OF HCV

Effective investigation of the natural history of a disease requires specific information including the identification of disease onset, method of differentiating between acute and chronic disease, and the ability to track disease morbidity and mortality without the influence of comorbid conditions and/or treatment (92). With regard to hepatitis C, the onset of disease is rarely known and patients often have comorbid conditions and available treatment options that can alter the natural course of the infection.

Controversy exists regarding the natural history of hepatitis C. While many experts view hepatitis C as a progressive disease with a high likelihood of advancing to cirrhosis, hepatocellular carcinoma, and death; others consider this virus to be more variable in nature, with the majority of patients “dying with the disease, not of the disease.” These discordant opinions arise from the presence of variable types of studies that have been reported, including retrospective, prospective, and retrospective–prospective studies. Additionally, diverse patient populations with regard to host-related factors (age, gender, race, route of transmission, comorbidities) and virus-related factors (genotype, viral load, quasispecies) have been studied – often with discordant results.

3.1. Chronic Hepatitis C

Acute hepatitis C is rarely symptomatic, thus most patients are unaware of the fact that they even contracted the illness, unless they can identify a recognized exposure. Chronic hepatitis C is defined as the persistence of HCV RNA viremia for at least 6 months. Potential clinical outcomes for persons with chronic hepatitis C include cirrhosis, hepatocellular carcinoma, and death.

Progression from acute to chronic HCV occurs in 54–90% patients (28, 93–99). This variability is likely due to diverse study designs and patient populations. Thomas et al. reported that viral clearance was significantly more common in persons of non-black race and negative
HIV status. An association (although not statistically significant) was noted between viral clearance, female gender, age under 45 years, and coinfection with hepatitis B. There was no association between persistent viremia and weekly alcohol use or the frequency of intravenous drug use (93). In an analysis of 43 acute HCV infections, Villano and colleagues also reported that viral clearance was more common among non-black individuals, in addition to persons with jaundice and a lower peak viral load. Persons with undetectable viral load had no evidence of biochemical disease after clearance of infection. It should be noted, however, that persons with chronic hepatitis C often had normal transaminases at some point during the course of chronic infection (94). Rodger et al. compared HCV-RNA-positive persons with HCV-RNA-negative persons to determine factors linked to chronic infection. They found that a longer duration and increased frequency of intravenous drug use, as well as an increased average lifetime consumption of alcohol were inversely associated with clearance of infection (99). Vogt et al. found that younger age at time of infection may be related to viral clearance (98). This factor may have contributed to the relatively low rate of chronic HCV in the population studied by Rodger, as the mean age of the study subjects at the time of infection was less than 22 years (99).

3.2. Cirrhosis, Hepatocellular Cancer, and Liver-Related Death

While some studies show frequent progression of chronic HCV to cirrhosis, hepatocellular carcinoma, and death (95, 100–106), others report these outcomes as less common occurrences (28, 93, 98, 99, 107, 108). The CDC estimates that up to 20% of chronic HCV infections lead to cirrhosis over a period of 20–30 years. Poynard et al. performed a study using serial biopsies or a single biopsy with a presumed date of infection based on identified risk factors and reported that persons infected with HCV can be differentiated into three categories with regard to fibrosis progression without treatment: rapid fibrosers (33% of persons) who progress to cirrhosis in <20 years; intermediate fibrosers (36% of persons) who develop cirrhosis over 30 years; and slow fibrosers (31% of persons) who may progress to cirrhosis after >50 years of infection (109).

Numerous studies have been performed to evaluate risks of HCV-related morbidity and mortality. These evaluations are dependent on the type of study performed, host-related factors, and virus-related factors. This point is illustrated in a review by Freeman and colleagues, which analyzed 33 liver clinic series; 5 posttransfusion cohorts; 10 blood
donor cohorts; and 9 community-based cohorts. Development of cirrhosis after 20 years of infection was 22% for the liver clinic series; 24% for posttransfusion studies; 4% for blood donor studies; and 7% for community-based studies. Older age at the time of HCV infection, male gender, and heavy alcohol intake also correlated with a more rapid progression to cirrhosis (110). Limitations of studies on fibrosis progression include sample variability of liver biopsies, referral bias with inclusion of patients with severe liver disease, and inaccurate estimates of duration of infection.

3.2.1. STUDY DESIGN

Retrospective Studies

Initial studies of chronic hepatitis C natural history involved retrospective analysis of patients referred to academic centers. The advantage of these studies is that a long duration of infection can be studied and the roles of various factors can be evaluated. Disadvantages of these studies include an estimated date of exposure and a strong selection bias as this patient population is more likely to have clinically evident liver disease, resulting in referral to an academic liver center. Several retrospective studies have included patients with a presumed 20–30 years of infection and have shown that 20–51% of patients with chronic HCV progress to cirrhosis, 2–11% develop hepatocellular carcinoma, and 4–15% die of liver-related causes (100, 102–104). Bjoro and colleagues studied 17 Norwegian patients with primary hypogammaglobulinemia who contracted HCV infection as a result of transfusion with contaminated immune globulin from 1982 to 1986. Six patients had histological evidence of cirrhosis, and two went on to die of liver failure. The authors suggest that chronic HCV in the setting of primary hypogammaglobulinemia was associated with a greater morbidity and mortality when compared to a “healthy population” with chronic HCV (103).

- Tong and colleagues followed 131 patients who acquired HCV via blood transfusion, an average of 22 years prior to referral to a tertiary care center. Based on liver biopsy or abnormal coagulation parameters, 67 patients (51%) were cirrhotic. Upon entry into the study, seven patients (5.3%) had hepatocellular carcinoma, while an additional seven patients (5.3%) developed hepatocellular carcinoma during an average 4-year follow-up. Nineteen patients (14.5%) died of liver-related causes, including eight from cirrhosis complications and 11 from hepatocellular carcinoma. Persons who contracted HCV before age 50 developed cirrhosis and hepatocellular cancer at a slower rate as compared to persons who received blood transfusions after age 50 (100).
Yano and colleagues from Japan studied liver biopsies of 70 patients with chronic HCV, acquired either sporadically or via blood transfusion. During follow-up, 35 patients (50%) developed histological evidence of cirrhosis.

Niederau and colleagues followed 838 patients with a history of chronic HCV referred to an academic hepatology clinic for potential antiviral treatment. Of 580 patients who had undergone liver biopsy, 130 had histological evidence of cirrhosis at entry, while an additional 11 unbiopsied patients had clinical evidence of cirrhosis. During a follow-up of approximately 4 years, an additional 26 patients developed manifestations of cirrhosis, while 17 patients developed hepatocellular carcinoma and 31 patients died of liver-related disease (13 of whom had hepatocellular carcinoma). The authors noted an increased mortality in patients with chronic HCV who had cirrhosis, or greater than 15 years of infection. Long disease duration, excessive alcohol use, history of intravenous drug use, and old age also contributed to a decreased complication-free survival. A drawback to the study was the inclusion of patients who had been treated with interferon, thus making it difficult to study the natural history without confounding factors (104).

**Prospective Studies**

Prospective studies involve patients with recognized acute hepatitis who are followed to assess for the development of liver-related morbidity and mortality. Advantages include a known time of exposure and probable mode of infection, whereas disadvantages include a shorter duration of follow-up. Among patients followed in several prospective studies, 5–25% progressed to cirrhosis, 0–1.2% developed hepatocellular cancer, and 1.2–6% died of liver-related disease over a follow-up of 13–24 years (28, 101, 105, 106).

Di Bisceglie and colleagues prospectively studied 33 non-A, non-B hepatitis patients who received blood transfusions perioperatively at the time of cardiac surgery between 1972 and 1983 at the National Institutes of Health (NIH), as well as six additional NIH patients who contracted acute hepatitis from blood transfusions. Ninety percent of these patients had chronic hepatitis C. Eight patients (20.5%) had histological evidence of cirrhosis with an average of 4.2 years after blood transfusion.

Mattsson and colleagues studied stored blood samples from 39 of 61 patients who had acute non-A, non-B hepatitis in Sweden in 1978. Sixteen patients had chronic hepatitis C. Liver biopsies were performed in eight patients within 13 years of the acute episode, and two patients had histological findings of cirrhosis. One patient died of liver-related disease but was not included in the analysis. Drawbacks to the study
included a short duration of follow-up and the possibility of underestimation of patients with cirrhosis, as not all were biopsied (106).

- Koretz and colleagues prospectively studied 80 patients with non-A, non-B hepatitis secondary to blood transfusions in the 1970s. Sixty-four of these patients were diagnosed with hepatitis C, 50 of whom were chronic. This study suggested that, based on life-table analysis, 20% of patients with chronic HCV could develop hepatic failure, defined by variceal bleeding, ascites, hepatic encephalopathy, coagulopathy, hypersplenism, or hypoalbuminemia. Liver biopsies were not performed in these patients. Drawbacks of this study were the variable duration of follow-up and the possibility of underestimation, based on exclusion of patients without clinically evident cirrhosis (101).

- Alter and colleagues prospectively studied 248 asymptomatic blood donors positive for anti-HCV. Liver biopsies were done in 81 HCV RNA-positive persons and 5% demonstrated cirrhosis. Three of these cirrhotic patients were discovered 27 years after their presumed exposure and one patient was found to have hepatocellular carcinoma 53 years after a blood transfusion. More severe disease was seen in patients with ALT elevations greater than twice the upper limit of normal (28).

Retrospective–Prospective Studies

Retrospective–prospective studies involve the identification of patients who previously developed a known acute hepatitis. These patients were studied retrospectively, enrolled, and followed prospectively for the development of liver-related morbidity and mortality. Over a follow-up of 15–45 years, these studies have generally shown lower rates of progression to cirrhosis (0.4–18.1%), hepatocellular carcinoma (0%), and death from liver-related causes (0.2–9.1%) in comparison to purely retrospective studies (93, 95, 98, 99, 107, 108).

- Vogt et al. compared 458 children under the age of 3, who underwent cardiac surgery in Germany prior to 1991, with 458 controls. When stored blood samples were tested, 67 patients (14.6%) who underwent cardiac surgery and three (0.7%) controls were anti-HCV positive. Thirty antibody-positive children (45%) had undetectable HCV RNA at a mean of 19.8 years after their first operation. Seventeen patients had liver biopsies, of which one, who had also been coinfected with HBV, was found to be cirrhotic. The authors concluded that clearance of HCV viremia was more common among children and progression of chronic HCV-related liver disease acquired at a young age was slower than older adults (98).

- Kenny-Walsh and colleagues evaluated 376 women with chronic HCV is likely secondary to transfusion of contaminated anti-D immunoglobulin. Three hundred and sixty-three infected women underwent liver
biopsies. Cirrhosis was found in 7 women, or 2% of biopsies, an average of 17 years after the initial transfusion. Three of these cirrhotic participants reported excessive alcohol consumption (108).

- Seeff et al. studied 8568 stored blood samples taken from healthy military recruits between 1948 and 1954 for evaluation of group A streptococcal infection and acute rheumatic fever. Seventeen persons were anti-HCV positive and 11 were HCV RNA positive. Of these 11 patients, one person had been diagnosed with cirrhosis and another had died of liver-related disease, 42 years after the blood sample was taken. Liver-related morbidity and all-cause mortality were slightly higher in the anti-HCV-positive group. There were no deaths attributed to hepatocellular carcinoma. Lower rates of cirrhosis, HCC, and liver-related death may have related to the fact that this was a young and healthy study population. Advantages of this study were an extended observation period in a healthy population, without comorbidities that could alter the course of HCV-related liver disease. Disadvantages included the possibility of false-negative anti-HCV results secondary to an extended period of serum specimen storage and a small cohort of patients with hepatitis C (95).

- Rodger and colleagues compared long-term outcomes of 98 persons with acute hepatitis C to 202 persons with acute hepatitis unrelated to HCV. Anti-HCV testing was performed on stored sera from 1971 to 1975 in Australia. The presumed route of HCV transmission was intravenous drug use, as opposed to other studies that focused on transfusion-associated HCV. Fifty-one patients with anti-HCV positivity were found to have chronic HCV based on HCV RNA testing. Normal liver tests were associated with a lower risk of long-term complications, a finding which has been observed in other studies as well (28, 111, 112). The authors concluded that outcomes of cirrhosis, hepatocellular cancer, and liver-associated death in the setting of chronic HCV after a follow-up of 25 years were less common than previously perceived. Although patients with anti-HCV positivity had a higher rate of mortality compared to the anti-HCV-negative group, these deaths were not related to HCV complications. A drawback to this study was that only 14% of anti-HCV-positive persons underwent liver biopsy, although hyaluronate levels were measured as a surrogate for fibrosis to reduce an underestimation of cirrhosis (99).

- Thomas and others studied 1667 patients with a history of intravenous drug use within 10 years of recruitment and anti-HCV positivity. Forty patients were categorized as having end-stage liver disease (ESLD), defined by clinical documentation of varices, ascites, or hepatic encephalopathy. Of these patients, 35 had died while one had received a liver transplant. Of patients without documented ESLD, 374 had died of non-liver-related causes. Liver biopsies were performed on
210 participants without clinical evidence of ESLD and cirrhosis was found in two persons. In addition, five patients who died without previously identified ESLD had evidence of cirrhosis on autopsy. ESLD was associated with age greater than 38, male sex, and heavy alcohol use. It did not correlate with HIV status, HBV status, moderate alcohol use, race, viral load, or viral genotype. The low incidence of ESLD in this cohort may be attributed to the restrictive definition of ESLD, without considering laboratory results suggestive of cirrhosis, as well as a relatively short duration of follow-up (93).

An endemic outbreak of hepatitis C in Germany in 1979 secondary to administration of contaminated anti-D immunoglobulin provided a patient population of 1016 women who were prospectively studied for 20 years by Weisse and colleagues. Of these women, 55% had evidence of chronic HCV infection (7% had not responded to interferon), while 42% had spontaneous clearance of virus and 3% responded to interferon. Four participants had clinical evidence of cirrhosis; it was not seen in any of the 220 biopsy specimens obtained. Two patients died of liver disease; one patient had fulminant hepatitis B and the other was a chronic alcohol abuser. There were no cases of hepatocellular carcinoma (107).

3.2.2. HOST-RELATED FACTORS

Age

Several studies have suggested that younger age at the time of infection may protect against progression to cirrhosis, HCC, and liver-related mortality (93, 95, 98, 100, 109, 110, 113). As discussed previously, Vogt et al. evaluated young children who underwent cardiac surgery during their first 3 years of life and found that only 5.4% of children had histological evidence of cirrhosis after a follow-up of 17 years (98). Furthermore, two studies of young women who received contaminated immunoglobulin at median ages of 24 and 28 years showed that a relatively low number (0.4–2.0%) had cirrhosis after a follow-up of 17–20 years (107, 108). Even among Seeff’s study of young (age < 25) military recruits with chronic hepatitis C, two of 11 patients were cirrhotic after a 45-year follow-up (95). Ryder and colleagues performed serial liver biopsies in 214 patients with chronic hepatitis C to assess progression of fibrosis. Results showed that older age of patients and presence of fibrosis on the initial biopsy were associated with progression of fibrosis (114). These results were similar to Svirltlih et al., who performed liver biopsies in 144 patients with chronic hepatitis C and found that age over 40 years at the time of liver biopsy was associated with an increased Ishak fibrosis score (115). What is not known is whether the rate of progression increases as these young persons age over time,
possibly explained by the inability of the immune system to contain the virus as it ages (109).

**Gender**

HCV is more commonly eliminated by women (107–110, 116). Poy-nard and Freeman conducted separate studies and found that male gender, in addition to alcohol consumption and older age at infection, was associated with fibrosis progression (109, 110). Yamakawa and colleagues conducted a study to compare progression to chronic hepatitis C in men and women in a town in Japan. They found that although anti-HCV positivity did not differ between genders, the proportion of anti-HCV-positive participants who were also HCV-RNA positive was higher in men (78.2%) than in women (67.3%) (116). Several studies have postulated that this may relate to the anti-fibrotic effects of estrogen (117–119). Yasuda and colleagues induced hepatic fibrosis in male and female rats with administration of dimethylnitrosamine and found that estradiol inhibited fibrogenesis by preventing proliferation of hepatic stellate cells which are responsible for collagen synthesis, as well as contributing antioxidant activity (118).

**Race**

Relative to Caucasians, African-Americans are 2–3 times more likely to be anti-HCV positive and less likely to undergo spontaneous clearance of HCV viremia (5). In addition, African-Americans are more prone to develop complications of cirrhosis, including hepatocellular carcinoma, and have lower response rates to antiviral treatment (120–122). However, their rates of fibrosis progression are slower than Caucasians (120, 123, 124). Bonacini and colleagues studied the histological progression of 291 chronic HCV patients (53 African-American, 116 Caucasian) with regard to duration of infection and race. The estimated rate of fibrosis among African-Americans was 0.055 stages per year compared to 0.096 stages per year among Caucasians (120). This disparity may be explained by variable immune responses between both groups (123).

**HIV Coinfection**

In the United States, 30% of HIV-positive patients are also infected with HCV (125). In the setting of HIV infection, HCV fibrosis is accelerated (126, 127). Benhamou and colleagues compared the rates of fibrosis progression in 122 anti-HIV positive, anti-HCV-positive persons and 122 anti-HIV negative, anti-HCV-positive persons. They found a Metavir fibrosis score of 2–4 in 60% of coinfected patients as compared to 47% of HCV-monoinfected patients. The median fibrosis
progression rate (ratio between fibrosis stage and HCV duration) was 0.153 fibrosis units per year in the former and 0.106 fibrosis units per year in the latter. Multivariate analysis showed that HIV seropositivity, CD4 count <200, age >25 at the time of HCV infection, and alcohol >50 g/day were all associated with a faster rate of fibrosis progression (126). Fibrosis progression may be linked to a weaker CD8+ T-cell response to HCV antigens in the setting of HIV (128). HAART therapy slows the progression of fibrosis through immune reconstitution, and possibly, HIV viral load suppression (129, 130).

**HBV Coinfection**

Several studies have reported that HBV infection in the setting of chronic HCV leads to a worsening of liver disease and increased risk for hepatocellular carcinoma (131–133). However, Senturk et al. evaluated 51 patients with HCV and HBV coinfection and found that clinical or histological findings did not differ between the group with HBV/HCV coinfection as compared to the groups with single infections. The authors did find that HCV was the dominant infection (134). Other studies have shown that hepatitis C tends to reduce HBV virus replication (131, 135, 136). The AASLD recommends that non-HBV immune patients with chronic HCV should be vaccinated against hepatitis B (137).

**Metabolic Syndrome**

The metabolic syndrome is defined as a constellation of factors including hypertension, abdominal obesity, diabetes mellitus, dyslipidemia, and nonalcoholic fatty liver disease (NAFLD). NAFLD comprises a histological spectrum of disease ranging from steatosis alone to steatohepatitis to fibrosis, and in some cases, cirrhosis. Extensive research has been conducted to examine correlations between the metabolic syndrome and hepatitis C. The metabolic syndrome can promote progression of hepatic fibrosis and a decreased response to antiviral therapy (138). The prime mechanism responsible for the metabolic syndrome is insulin resistance (139). Insulin resistance leads to hepatic steatosis and stimulates inflammation, resulting in steatohepatitis and possibly fibrosis (138). Other theories describe oxidative stress as a necessary “second-hit” in the development of steatohepatitis. Oxidative stress initiates lipid peroxidation, resulting in stellate cell activation and synthesis of type I collagen (138, 140). Leptin, a peptide primarily produced by adipose tissue, may also play a role in fibrinogenesis (139). Of note, hepatic steatosis itself may cause activation of stellate cells (139). The AASLD Practice Guidelines state that patients with a BMI
>25 kg/m² in the setting of chronic HCV should make an effort to lose weight (137).

**Alcohol Consumption**

Heavy alcohol intake hastens progression to cirrhosis (93, 109, 110, 124, 141–144). Harris and colleagues found a fourfold increased risk for cirrhosis in the setting of increased alcohol consumption in a population of patients with transfusion-associated HCV (124). Ostapowicz et al. studied 234 patients in Australia with chronic hepatitis C and found that greater alcohol use during HCV infection and an increased cumulative consumption of alcohol were associated with progression of liver disease (142). Pessione et al. found a dose–response relationship between self-reported past and present alcohol consumption and HCV viremia (143). They also reported a link between fibrosis and prior alcohol use (143). Corrao noted a synergistic effect of alcohol on chronic HCV at doses of 75–100 g/day and suggested that patients without signs of liver disease could consume <50 g alcohol daily (141). Poynard and colleagues found that daily consumption of alcohol >50 g is a risk factor for advanced liver disease (109), while Hezode reported that even 21–50 g/day can have a negative impact on women with chronic HCV (145). The physiological basis for the detrimental effects of alcohol include immune dysregulation, proinflammatory and profibrotic cytokine stimulation, oxidative stress, and steatosis (146). Seeff advises against “alcoholism” in the setting of chronic HCV (147). AASLD guidelines recommend that patients with chronic HCV should minimize alcohol consumption, and not exceed 50 g/day (137).

**Tobacco Use**

Tobacco use is suspected to promote fibrosis in the setting of chronic HCV (148, 149). Pessione and colleagues identified smoking as an independent risk factor for fibrosis in a study of 310 patients with chronic HCV who underwent a liver biopsy. In addition, smoking has been linked to hepatocellular carcinoma in the setting of chronic hepatitis (150, 151). Hepatotoxic compounds in cigarettes may account for this progression (152).

### 3.2.3. Virus-Related Factors

#### Mode of Transmission

Several studies have suggested that the mode of transmission of HCV may affect progression to complications, with blood transfusions associated with increased risk of cirrhosis possibly related to a higher initial inoculum (99–101, 105, 106, 153). Transfusion studies have shown a 20% rate of progression to cirrhosis at 20 years (100, 147, 154), while
studies of intravenous drug users show lower rates of serious sequelae (99). Gordon and colleagues evaluated 463 patients at an nonurban medical center with chronic hepatitis C and available liver histology, of which 215 (45%) were transfusion recipients, 195 (42%) acquired HCV mainly through intravenous drug use, and 53 (13%) were without identified risks. With a median follow-up duration of 21 years, 173 (37%) patients were cirrhotic and 118 (68%) of them were transfusion recipients. The Kaplan–Meier cumulative risk for cirrhosis 25 years after HCV acquisition was 52.5% among transfusion recipients and 35% among intravenous drug users (155).

**Viral Load**

While some studies have suggested that an increased viral load is indicative of more advanced liver disease (156, 157), others have not revealed similar findings (142, 158–161). Adinolfi et al. studied liver biopsies of 298 patients with chronic hepatitis C and found that viral load was linked to grade of inflammation and stage of fibrosis in noncirrhotic patients. However, once patients advanced to cirrhosis, their viral loads declined (157). Fanning and colleagues examined liver biopsies of 77 young, healthy women with chronic HCV genotype 1b of 17 years duration with contaminated anti-D immunoglobulin as a source for infection. The authors discovered a weak but statistically significant correlation between viral load and hepatic inflammation. However, viral load was not associated with the degree of liver fibrosis (161).

**Virus Genotype**

There are conflicting data regarding the effect of virus genotype on fibrosis progression. While some studies have suggested that specific genotypes are associated with progression of fibrosis (162–164), others have not found such a correlation (109, 165, 166). Kobayashi and colleagues evaluated 136 patients with chronic hepatitis C who had two liver biopsies performed 5 years apart. Ninety-six patients were infected with genotype 1 virus, while 40 patients had genotype 2 virus. Genotype 1 infected patients had a higher initial viral load and repeat liver biopsy showed worsening of liver histology in terms of grade and stage of disease. The authors suggested that genotype 1b disease was more “pathogenic” than genotype 2 disease (167). In contrast, Mahaney and colleagues reported more severe liver disease in patient infected with genotype 2 virus (168). Mihm et al. examined 90 liver biopsies of patients with chronic HCV genotypes 1a, 1b, or 3a and found that fibrosis was more common in genotype 1b infection, while steatosis was seen more frequently with genotype 3a infection. The authors
Table 4
Factors that influence the progression of chronic HCV

<table>
<thead>
<tr>
<th>Factor</th>
<th>Effect on progression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at infection</td>
<td>Younger age, slower rate of progression</td>
</tr>
<tr>
<td>Sex</td>
<td>Female, slower rate of progression</td>
</tr>
<tr>
<td>Race</td>
<td>AA, slower rate of progression</td>
</tr>
<tr>
<td>HIV or HBV coinfection</td>
<td>More rapid progression</td>
</tr>
<tr>
<td>Metabolic syndrome</td>
<td>More rapid progression</td>
</tr>
<tr>
<td>Alcohol consumption</td>
<td>More rapid progression</td>
</tr>
<tr>
<td>Tobacco use</td>
<td>More rapid progression suggested</td>
</tr>
<tr>
<td>Mode of transmission</td>
<td>Transfusion: higher inoculum, more rapid rate of progression</td>
</tr>
<tr>
<td>Virus concentration</td>
<td>Inconclusive evidence</td>
</tr>
<tr>
<td>Virus genotype</td>
<td>Inconclusive evidence, 1b may be associated with more severe disease</td>
</tr>
<tr>
<td>Virus quasispecies</td>
<td>No evidence</td>
</tr>
</tbody>
</table>

Speculated that the increase in fibrosis seen in genotype 1b disease could be attributed to an older age population and a longer duration of disease (169).

**Virus Quasispecies**

The presence of HCV quasispecies has been compared in patients with resolution of acute hepatitis and the development of chronic hepatitis. Human studies suggest that the development of heterogeneous quasispecies is linked to progression to chronic hepatitis (170). There is no evidence that quasispecies affect advancement of liver disease in the setting of chronic hepatitis C (92) (Table 4).

4. CONCLUSIONS

Chronic hepatitis C is associated with progression to cirrhosis, hepatocellular carcinoma, and liver-related death. It is difficult to clearly define morbidity and mortality risk as variable study types and patient populations yield conflicting results. It is therefore important to takes these factors into consideration when analyzing studies appropriately.
Retrospective studies show the highest rates of morbidity and mortality, followed by prospective studies and retrospective–prospective studies. The actual rates likely lie somewhere in between the extremes of these three categories of study. Progression of HCV is hastened when acquired via blood transfusion; at an older age; in males; in non-African-Americans; in the setting of excessive alcohol (and possibly tobacco) use; and, in persons with HIV and/or HBV coinfection or features of metabolic syndrome. It is controversial if HCV viral load and genotype affect the evolution of disease.

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