- Intravenous drug abuse (54%)
- Multiple sex partners (36%)
- Having had surgery within the last 6 month (16%)
- Needle stick injury (10%)
- Multiple contacts with an HCV-infected person (10%)
- Employment in medical or dental fields (1.5%)
- Unknown (32%)

Currently, rate of transmission of HCV by blood transfusion is close to zero in the United States; the risk for acquiring HCV by needle stick is about six times higher than the same risk for acquiring HIV (1.8% vs 0.3%). For children, the major route of infection is perinatal, but this route of infection with HCV is much lower than for HBV (6% vs. 20%). Note that patients may have multiple risk factors (the total of the aforementioned listed risks is greater than 100%), but *one third of individuals have no identifiable risk factors*, an enduring hepatologic mystery.

HCV, discovered in 1989, is a member of the Flaviviridae family. It is a small, enveloped, single-stranded RNA virus with a 9.6-kilobase (kb) genome that codes for a single polyprotein with one open reading frame, which is subsequently processed into functional proteins. Because of the low fidelity of the HCV RNA polymerase, the virus is inherently unstable, giving rise to multiple genotypes and subtypes. Indeed, *within any given individual, HCV exists as closely related genetic variants known as quasispecies.*

Over time, dozens of quasispecies can be detected within one individual all derived from the original HCV strain that infected the patient. The E2 protein of the envelope is the target of many anti-HCV antibodies but is also the most variable region of the entire viral genome, enabling emergent virus strains to escape from neutralizing antibodies. This genomic instability and antigenic variability have seriously hampered efforts to develop an HCV vaccine. In particular, *elevated titers of anti-HCV IgG occurring after an active infection do not confer effective immunity.* A characteristic feature of HCV infection, therefore, is repeated bouts of hepatic damage, the result of reactivation of a preexisting infection or emergence of an endogenous, newly mutated strain.

The incubation period for HCV hepatitis ranges from 4 to 26 weeks, with a mean of 9 weeks. In about 85% of individuals, the clinical course of the acute infection is asymptomatic and typically missed. HCV RNA is detectable in blood for 1 to 3 weeks, coincident with elevations in serum transaminases. In symptomatic acute HCV infection, anti-HCV antibodies are detected in only 50% to 70% of patients; in the remaining patients, the anti-HCV antibodies emerge after 3 to 6 weeks. The clinical course of acute HCV hepatitis is milder than that of HBV; rare cases may be severe and indistinguishable from HAV or HBV hepatitis. It is not known why only a small minority of individuals are capable of clearing HCV infection.

Persistent infection and chronic hepatitis are the hallmarks of HCV infection, despite the generally asymptomatic nature of the acute illness. In contrast to HBV, chronic disease occurs in the majority of HCV-infected individuals (80% to 90%) and cirrhosis eventually occurs in as many as a 20% of individuals with chronic HCV infection. The mechanisms that lead to the chronicity of HCV infection are not well understood, but it is clear that the virus has developed multiple strategies to evade host antiviral immunity. HCV is able to actively inhibit the IFN-mediated cellular antiviral response at multiple steps, including toll-like receptor signaling in response to viral RNA recognition and signaling downstream of IFN receptors that would otherwise have antiviral effects.

In more than 90% of individuals with chronic HCV infection, circulating HCV RNA persists despite the presence of antibodies (Fig. 18-13). Hence, in persons with chronic hepatitis, HCV RNA testing must be performed to assess viral replication and to confirm the diagnosis of HCV infection. A clinical feature that is quite characteristic of chronic HCV infection is persistent elevations in serum aminotransferases. Their levels wax and wane but almost never become normal. Even rare patients with normal transaminases are at risk for developing permanent liver damage. Therefore, any individual with detectable HCV

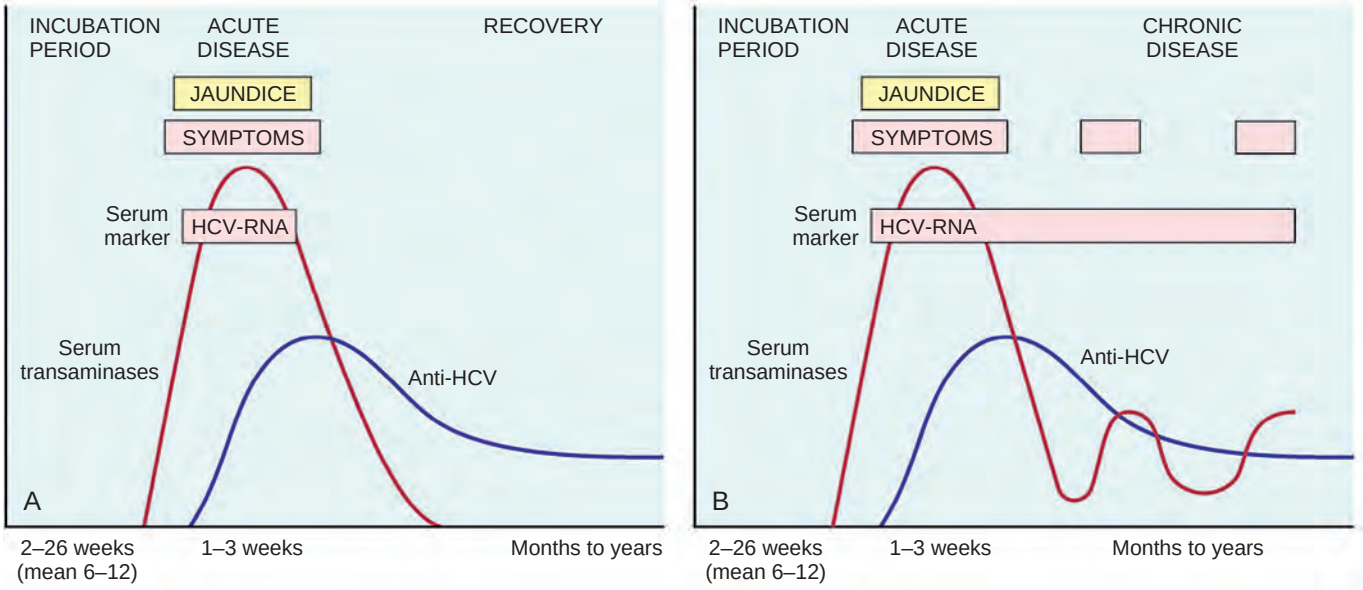

Figure 18-13 Temporal changes in serologic markers in hepatitis C viral infection. **A,** Acute infection with resolution. **B,** progression to chronic infection.