332 Acute Viral Hepatitis

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Acute viral hepatitis is a systemic infection affecting the liver predominantly. Almost all cases of acute viral hepatitis are caused by one of five viral agents: hepatitis A virus (HAV), hepatitis B virus (HBV), hepatitis C virus (HCV), the HBV-associated delta agent or hepatitis D virus (HDV), and hepatitis E virus (HEV). All these human hepatitis viruses are RNA viruses, except for hepatitis B, which is a DNA virus but replicates like a retrovirus. Although these agents can be distinguished by their molecular and antigenic properties, all types of viral hepatitis produce clinically similar illnesses. These range from asymptomatic and inapparent to fulminant and fatal acute infections common to all types, on the one hand, and from subclinical persistent infections to rapidly progressive chronic liver disease with cirrhosis and even hepatocellular carcinoma, common to the bloodborne types (HBV, HCV, and HDV), on the other.

VIROLOGY AND ETIOLOGY

Hepatitis A HAV is a nonenveloped 27-nm, heat-, acid-, and ether-resistant RNA virus in the *Hepatovirus* genus of the picornavirus family **(Fig. 332-1)**. Its virion contains four capsid polypeptides, designated VP1–VP4, which are cleaved posttranslationally from the polyprotein product of a 7500-nucleotide genome. Inactivation of viral activity can be achieved by boiling for 1 min, by contact with formaldehyde and chlorine, or by ultraviolet irradiation. Despite nucleotide sequence variation of up to 20% among isolates of HAV, and despite the recognition of four genotypes affecting humans, all strains of this virus are immunologically indistinguishable and belong to one serotype. Human HAV can infect and cause hepatitis in chimpanzees, tamarins (marmosets), and several monkey species. Recently, a hepatotropic *Hepatovirus* related to, and likely to have shared common evolutionary ancestry with, human HAV has been identified in several species of harbor seals, albeit without histologic evidence for liver injury or inflammation. Hepatitis A has an incubation period of ~4 weeks. Its replication is limited to the liver, but the virus is present in the liver, bile, stools, and blood during the late incubation period and acute preicteric/presymptomatic phase of illness. Despite slightly longer persistence of virus in the liver, fecal shedding, viremia, and infectivity diminish rapidly once jaundice becomes apparent. HAV can be cultivated reproducibly in vitro.

Antibodies to HAV (anti-HAV) can be detected during acute illness when serum aminotransferase activity is elevated and fecal HAV shedding is still occurring. This early antibody response is predominantly of the IgM class and persists for several (~3) months, rarely for 6–12 months. During convalescence, however, anti-HAV of the IgG class becomes the predominant antibody **(Fig. 332-2)**. Therefore, the diagnosis of hepatitis A is made during acute illness by demonstrating anti-HAV of the IgM class. After acute illness, anti-HAV of the IgG class remains detectable indefinitely, and patients with serum anti-HAV are immune to reinfection. Neutralizing antibody activity parallels the appearance of anti-HAV, and the IgG anti-HAV present in immune globulin accounts for the protection it affords against HAV infection.

Hepatitis B HBV is a DNA virus with a remarkably compact genomic structure; despite its small, circular, 3200-bp size, HBV DNA codes for four sets of viral products with a complex, multiparticle structure. HBV achieves its genomic economy by relying on an efficient strategy of encoding proteins from four overlapping genes: S, C, P, and X **(Fig. 332-3)**, as detailed below. Once thought to be unique among viruses, HBV is now recognized as one of a family of animal viruses, hepadnaviruses (hepatotropic DNA viruses), and is classified as hepadnavirus type 1. Similar viruses infect certain species of woodchucks, ground and tree squirrels, and Pekin ducks, to mention the most carefully characterized; genetic evidence of ancient HBV-like virus

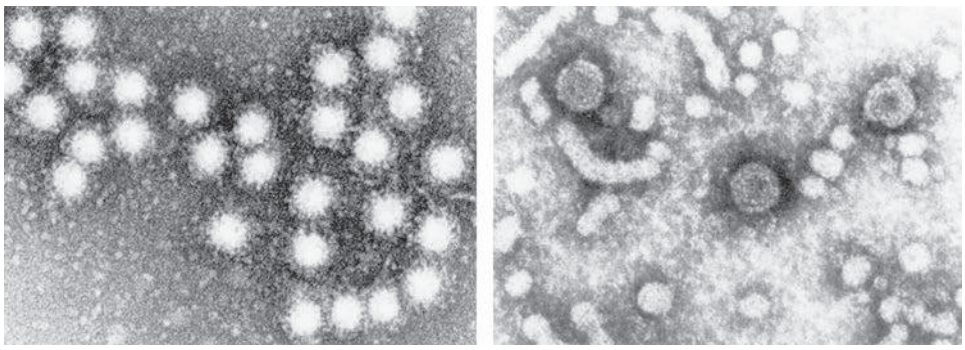

FIGURE 332-1 Electron micrographs of hepatitis A virus particles and serum from a patient with hepatitis B. ***Left:*** 27-nm hepatitis A virus particles purified from stool of a patient with acute hepatitis A and aggregated by antibody to hepatitis A virus. ***Right:*** Concentrated serum from a patient with hepatitis B, demonstrating the 42-nm virions, tubular forms, and spherical 22-nm particles of hepatitis B surface antigen. 132,000×. (Hepatitis D resembles 42-nm virions of hepatitis B but is smaller, 35–37 nm; hepatitis E resembles hepatitis A virus but is slightly larger, 32–34 nm; hepatitis C has been visualized as a 55-nm particle.)

forbears has been found in fossils of ancient birds, and a HBV-like virus has been identified in contemporary fish. Like HBV, all have the same distinctive three morphologic forms, have counterparts to the envelope and nucleocapsid virus antigens of HBV, replicate in the liver but exist in extrahepatic sites, contain their own endogenous DNA polymerase, have partially double-strand and partially single-strand genomes, are associated with acute and chronic hepatitis and hepatocellular carcinoma, and rely on a replicative strategy unique among DNA viruses but typical of retroviruses. Entry of HBV into hepatocytes is mediated by binding to the sodium taurocholate cotransporting polypeptide receptor. Instead of DNA replication directly from a DNA template, hepadnaviruses rely on reverse transcription (effected by the DNA polymerase) of minus-strand DNA from a "pregenomic" RNA intermediate. Then, plus-strand DNA is transcribed from the minus-strand DNA template by the DNA-dependent DNA polymerase and converted in the hepatocyte nucleus to a covalently closed circular DNA, which serves as a template for messenger RNA and pregenomic RNA. Viral proteins are translated by the messenger RNA, and the proteins and genome are packaged into virions and secreted from the hepatocyte. Although HBV is difficult to cultivate in vitro in the conventional sense from clinical material, several cell lines have been transfected with HBV DNA. Such transfected cells support in vitro replication of the intact virus and its component proteins.

VIRAL PROTEINS AND PARTICLES Of the three particulate forms of HBV (Table 332-1), the most numerous are the 22-nm particles, which appear as spherical or long filamentous forms; these are antigenically indistinguishable from the outer surface or envelope protein of HBV and are thought to represent excess viral envelope protein. Outnumbered in serum by a factor of 100 or 1000 to 1 compared with the spheres and tubules are large, 42-nm, double-shelled spherical particles, which represent the intact hepatitis B virion (Fig. 332-1). The envelope protein expressed on the outer surface of the virion and on the smaller spherical and tubular structures is referred to as *hepatitis B surface antigen* (HBsAg). The concentration of HBsAg and virus particles in the blood may reach 500 μg/mL and 10 trillion particles per milliliter, respectively. The envelope protein, HBsAg, is the product of the S gene of HBV.

Envelope HBsAg subdeterminants include a common group-reactive antigen, *a*, shared by all HBsAg isolates and one of several subtype-specific antigens—*d* or *y*, *w* or *r*—as well as other specificities. Hepatitis B isolates fall into one of at least 8 subtypes and 10 genotypes (A–J). Geographic distribution of genotypes and subtypes varies; genotypes A (corresponding to subtype *adw*) and D (*ayw*) predominate in the United States and Europe, whereas genotypes B (*adw*) and C (*adr*) predominate in Asia. Clinical course and outcome are independent of subtype, but genotype B appears to be associated with less rapidly progressive liver disease and cirrhosis and a lower likelihood, or delayed appearance, of hepatocellular carcinoma than genotype C or D. Patients with genotype A are more likely to clear circulating viremia and achieve *hepatitis B e antigen* (HBeAg) and HBsAg seroconversion, both spontaneously and in response to antiviral therapy. In addition, "precore" mutations are favored by certain genotypes (see below).

Upstream of the S gene are the pre-S genes (Fig. 332-3), which code for pre-S gene products, including receptors on the HBV surface for polymerized human serum albumin and for hepatocyte membrane proteins. The pre-S region actually consists of both pre-S1 and pre-S2. Depending on where translation is initiated, three potential HBsAg gene products are synthesized. The protein product of the S gene is HBsAg (*major protein*), the product of the S region plus the adjacent pre-S2 region is the *middle protein*, and the product of the pre-S1 plus pre-S2 plus S regions is the *large protein*. Compared with the smaller spherical and tubular particles of HBV, complete 42-nm virions are enriched in the large protein. Both pre-S proteins and their respective antibodies can be detected during HBV infection, and the period of pre-S antigenemia appears to coincide with other markers of virus replication,

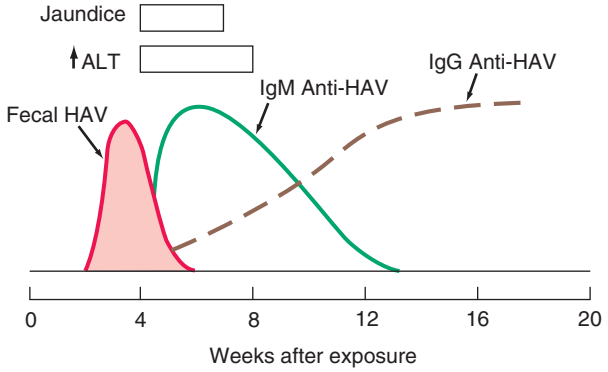

FIGURE 332-2 Scheme of typical clinical and laboratory features of hepatitis A virus (HAV). ALT, alanine aminotransferase.

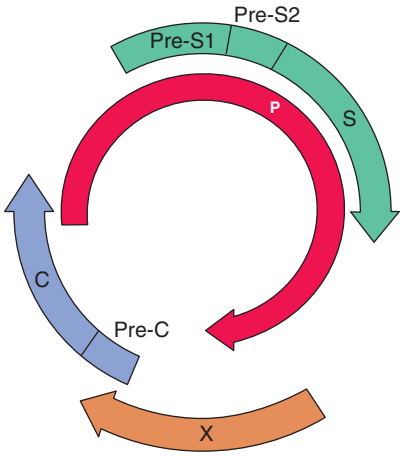

FIGURE 332-3 Compact genomic structure of hepatitis B virus (HBV). This structure, with overlapping genes, permits HBV to code for multiple proteins. The S gene codes for the "major" envelope protein, HBsAg. Pre-S1 and pre-S2, upstream of S, combine with S to code for two larger proteins, "middle" protein, the product of pre-S2 + S, and "large" protein, the product of pre-S1 + pre-S2 + S. The largest gene, P, codes for DNA polymerase. The C gene codes for two nucleocapsid proteins, HBeAg, a soluble, secreted protein (initiation from the pre-C region of the gene), and HBcAg, the intracellular core protein (initiation after pre-C). The X gene codes for HBxAg, which can transactivate the transcription of cellular and viral genes; its clinical relevance is not known, but it may contribute to carcinogenesis by binding to p53.

TABLE 332-1 Nomenclature and Features of Hepatitis Viruses

HEPATITIS TYPE	VIRUS PARTICLE, nm	MORPHOLOGY	GENOME[a]	CLASSIFICATION	ANTIGEN(s)	ANTIBODIES	REMARKS
HAV	27	Icosahedral nonenveloped	7.5-kb RNA, linear, ss, +	Hepatovirus	HAV	Anti-HAV	Early fecal shedding Diagnosis: IgM anti-HAV Previous infection: IgG anti-HAV
HBV	42	Double-shelled virion (surface and core) spherical	3.2-kb DNA, circular, ss/ds	Hepadnavirus	HBsAg HBcAg HBeAg	Anti-HBs Anti-HBc Anti-HBe	Bloodborne virus; carrier state Acute diagnosis: HBsAg, IgM anti-HBc Chronic diagnosis: IgG anti-HBc, HBsAg Markers of replication: HBeAg, HBV DNA Liver, lymphocytes, other organs
	27	Nucleocapsid core			HBcAg HBeAg	Anti-HBc Anti-HBe	Nucleocapsid contains DNA and DNA polymerase; present in hepatocyte nucleus; HBcAg does not circulate; HBeAg (soluble, nonparticulate) and HBV DNA circulate—correlate with infectivity and complete virions
	22	Spherical and filamentous; represents excess virus coat material			HBsAg	Anti-HBs	HBsAg detectable in >95% of patients with acute hepatitis B; found in serum, body fluids, hepatocyte cytoplasm; anti-HBs appears following infection—protective antibody
HCV	Approx. 50–80	Enveloped	9.4-kb RNA, linear, ss, +	Hepacivirus	HCV core antigen	Anti-HCV	Bloodborne agent, formerly labeled non-A, non-B hepatitis Acute diagnosis: anti-HCV, HCV RNA Chronic diagnosis: anti-HCV, HCV RNA; cytoplasmic location in hepatocytes
HDV	35–37	Enveloped hybrid particle with HBsAg coat and HDV core	1.7-kb RNA, circular, ss, –	Resembles viroids and plant satellite viruses (genus Deltavirus)	HBsAg HDAg	Anti-HBs Anti-HDV	Defective RNA virus, requires helper function of HBV (hepadnaviruses); HDV antigen (HDAg) present in hepatocyte nucleus Diagnosis: anti-HDV, HDV RNA; HBV/HDV co-infection—IgM anti-HBc and anti-HDV; HDV superinfection—IgG anti-HBc and anti-HDV
HEV	32–34	Nonenveloped icosahedral	7.6-kb RNA, linear, ss, +	Hepevirus	HEV antigen	Anti-HEV	Agent of enterically transmitted hepatitis; rare in the United States; occurs in Asia, Mediterranean countries, Central America Diagnosis: IgM/IgG anti-HEV (assays not routinely available); virus in stool, bile, hepatocyte cytoplasm

[a]ss, single-strand; ss/ds, partially single-strand, partially double-strand; –, minus-strand; +, plus-strand.

Note: See text for abbreviations.

as detailed below; however, pre-S proteins have little clinical relevance and are not included in routine serologic testing repertoires.

The intact 42-nm virion contains a 27-nm nucleocapsid core particle. Nucleocapsid proteins are coded for by the C gene. The antigen expressed on the surface of the nucleocapsid core is *hepatitis B core antigen* (HBcAg), and its corresponding antibody is anti-HBc. A third HBV antigen is HBeAg, a soluble, nonparticulate, nucleocapsid protein that is immunologically distinct from intact HBcAg but is a product of the same C gene. The C gene has two initiation codons: a precore and a core region (Fig. 332-3). If translation is initiated at the precore region, the protein product is HBeAg, which has a signal peptide that binds it to the smooth endoplasmic reticulum, the secretory apparatus of the cell, leading to its secretion into the circulation. If translation begins at the core region, HBcAg is the protein product; it has no signal peptide and is not secreted, but it assembles into nucleocapsid particles, which bind to and incorporate RNA, and which, ultimately, contain HBV DNA. Also packaged within the nucleocapsid core is a DNA polymerase, which directs replication and repair of HBV DNA. When packaging within viral proteins is complete, synthesis of the incomplete plus strand stops; this accounts for the single-strand gap and for differences in the size of the gap. HBcAg particles remain in the hepatocyte, where they are readily detectable by immunohistochemical staining and are exported after encapsidation by an envelope of HBsAg. Therefore, naked core particles do not circulate in the serum. The secreted nucleocapsid protein, HBeAg, provides a convenient, readily detectable, qualitative marker of HBV replication and relative infectivity.

HBsAg-positive serum containing HBeAg is more likely to be highly infectious and to be associated with the presence of hepatitis B virions (and detectable HBV DNA, see below) than HBeAg-negative or anti-HBe-positive serum. For example, HBsAg-positive mothers who are HBeAg-positive almost invariably (>90%) transmit hepatitis B infection to their offspring, whereas HBsAg-positive mothers with anti-HBe rarely (10–15%) infect their offspring.

Early during the course of acute hepatitis B, HBeAg appears transiently; its disappearance may be a harbinger of clinical improvement and resolution of infection. Persistence of HBeAg in serum beyond the first 3 months of acute infection may be predictive of the development of chronic infection, and the presence of HBeAg during chronic hepatitis B tends to be associated with ongoing viral replication, infectivity, and inflammatory liver injury (except during the early decades after perinatally acquired HBV infection; see below).

The third and largest of the HBV genes, the P gene (Fig. 332-3), codes for HBV DNA polymerase; as noted above, this enzyme has both DNA-dependent DNA polymerase and RNA-dependent reverse transcriptase activities. The fourth gene, X, codes for a small, nonparticulate protein, *hepatitis B x antigen* (HBxAg), that is capable of transactivating the transcription of both viral and cellular genes (Fig. 332-3). In the cytoplasm, HBxAg effects calcium release (possibly from mitochondria), which activates signal-transduction pathways that lead to stimulation of HBV reverse transcription and HBV DNA replication. Such transactivation may enhance the replication of HBV, leading to the clinical association observed between the expression of HBxAg and antibodies

to it in patients with severe chronic hepatitis and hepatocellular carcinoma. The transactivating activity can enhance the transcription and replication of other viruses besides HBV, such as HIV. Cellular processes transactivated by X include the human interferon-γ gene and class I major histocompatibility genes; potentially, these effects could contribute to enhanced susceptibility of HBV-infected hepatocytes to cytolytic T cells. The expression of X can also induce programmed cell death (apoptosis). The clinical relevance of HBxAg is limited, however, and testing for it is not part of routine clinical practice.

SEROLOGIC AND VIROLOGIC MARKERS After a person is infected with HBV, the first virologic marker detectable in serum within 1–12 weeks, usually between 8 and 12 weeks, is HBsAg **(Fig. 332-4)**. Circulating HBsAg precedes elevations of serum aminotransferase activity and clinical symptoms by 2–6 weeks and remains detectable during the entire icteric or symptomatic phase of acute hepatitis B and beyond. In typical cases, HBsAg becomes undetectable 1–2 months after the onset of jaundice and rarely persists beyond 6 months. After HBsAg disappears, antibody to HBsAg (anti-HBs) becomes detectable in serum and remains detectable indefinitely thereafter. Because HBcAg is intracellular and, when in the serum, sequestered within an HBsAg coat, naked core particles do not circulate in serum, and therefore HBcAg is not detectable routinely in the serum of patients with HBV infection. By contrast, anti-HBc is readily demonstrable in serum, beginning within the first 1–2 weeks after the appearance of HBsAg and preceding detectable levels of anti-HBs by weeks to months. Because variability exists in the time of appearance of anti-HBs after HBV infection, occasionally a gap of several weeks or longer may separate the disappearance of HBsAg and the appearance of anti-HBs. During this "gap" or "window" period, anti-HBc may represent the only serologic evidence of current or recent HBV infection, and blood containing anti-HBc in the absence of HBsAg and anti-HBs has been implicated in transfusion-associated hepatitis B. In part because the sensitivity of immunoassays for HBsAg and anti-HBs has increased, however, this window period is rarely encountered. In some persons, years after HBV infection, anti-HBc may persist in the circulation longer than anti-HBs. Therefore, isolated anti-HBc does not necessarily indicate active virus replication; most instances of isolated anti-HBc represent hepatitis B infection in the remote past. Rarely, however, isolated anti-HBc represents low-level hepatitis B viremia, with HBsAg below the detection threshold, and, occasionally, isolated anti-HBc represents a cross-reacting or false-positive immunologic specificity. Recent and remote HBV infections can be distinguished by determination of the immunoglobulin class of anti-HBc. Anti-HBc of the IgM class (IgM anti-HBc) predominates during the first 6 months after acute infection, whereas IgG anti-HBc is the predominant class of anti-HBc beyond 6 months. Therefore, patients with current or recent acute hepatitis B, including those in the anti-HBc window, have IgM anti-HBc in their serum. In patients who have recovered from hepatitis B in the remote past as well as those with chronic HBV infection, anti-HBc is predominantly of the IgG class. Infrequently, in ≤1–5% of patients with acute HBV infection, levels of HBsAg are too low to be detected; in such cases, the presence of IgM anti-HBc establishes the diagnosis of acute hepatitis B. When isolated anti-HBc occurs in the rare patient with chronic hepatitis B whose HBsAg level is below the sensitivity threshold of contemporary immunoassays (a low-level carrier), anti-HBc is of the IgG class. Generally, in persons who have recovered from hepatitis B, anti-HBs and anti-HBc persist indefinitely.

The temporal association between the appearance of anti-HBs and resolution of HBV infection as well as the observation that persons with anti-HBs in serum are protected against reinfection with HBV suggests that *anti-HBs is the protective antibody*. Therefore, strategies for prevention of HBV infection are based on providing susceptible persons with circulating anti-HBs (see below). Occasionally, in ~10% of patients with chronic hepatitis B, low-level, low-affinity anti-HBs can be detected. This antibody is directed against a subtype determinant different from that represented by the patient's HBsAg; its presence is thought to reflect the stimulation of a related clone of antibody-forming cells, but it has no clinical relevance and does not signal imminent clearance of hepatitis B. These patients with HBsAg and such nonneutralizing anti-HBs should be categorized as having chronic HBV infection.

The other readily detectable serologic marker of HBV infection, HBeAg, appears concurrently with or shortly after HBsAg. Its appearance coincides temporally with high levels of virus replication and reflects the presence of circulating intact virions and detectable HBV DNA (with the notable exception of patients with precore mutations who cannot synthesize HBeAg—see "Molecular Variants"). Pre-S1 and pre-S2 proteins are also expressed during periods of peak replication, but assays for these gene products are not routinely available. In self-limited HBV infections, HBeAg becomes undetectable shortly after peak elevations in aminotransferase activity, before the disappearance of HBsAg, and anti-HBe then becomes detectable, coinciding with a period of relatively lower infectivity (Fig. 332-4). Because markers of HBV replication appear transiently during acute infection, testing for such markers is of little clinical utility in typical cases of acute HBV infection. In contrast, markers of HBV replication provide valuable information in patients with protracted infections.

Departing from the pattern typical of acute HBV infections, in chronic HBV infection, HBsAg remains detectable beyond 6 months, anti-HBc is primarily of the IgG class, and anti-HBs is either undetectable or detectable at low levels (see "Laboratory Features") **(Fig. 332-5)**.

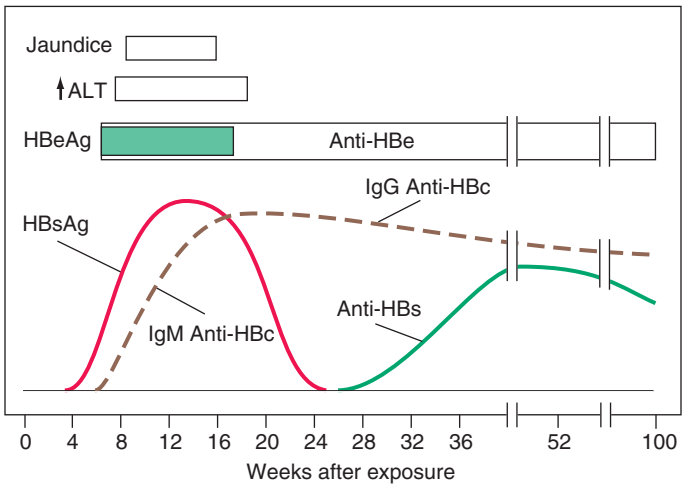

FIGURE 332-4 Scheme of typical clinical and laboratory features of acute hepatitis B. ALT, alanine aminotransferase.

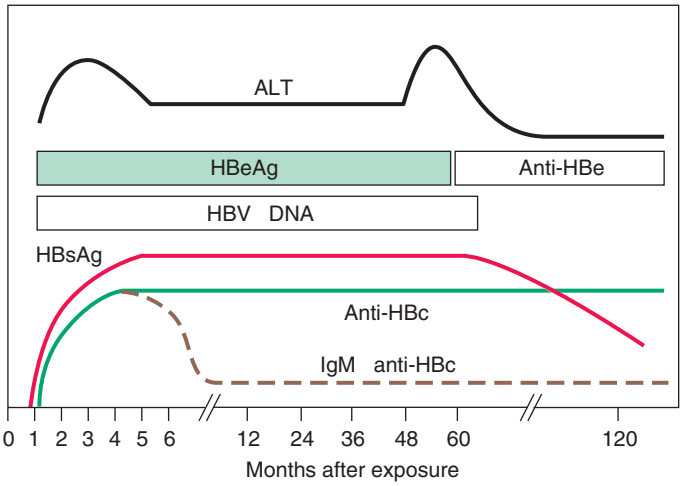

FIGURE 332-5 Scheme of typical laboratory features of wild-type chronic hepatitis B. HBeAg and hepatitis B virus (HBV) DNA can be detected in serum during the relatively *replicative phase* of chronic infection, which is associated with infectivity and liver injury. Seroconversion from the replicative phase to the relatively *nonreplicative phase* occurs at a rate of ~10% per year and is heralded by an acute hepatitis–like elevation of alanine aminotransferase (ALT) activity; during the nonreplicative phase, infectivity and liver injury are limited. In HBeAg-negative chronic hepatitis B associated with mutations in the precore region of the HBV genome, replicative chronic hepatitis B occurs in the absence of HBeAg.

During early chronic HBV infection, HBV DNA can be detected both in serum and in hepatocyte nuclei, where it is present in free or episomal form. This relatively highly *replicative stage* of HBV infection is the time of maximal infectivity and liver injury; HBeAg is a qualitative marker and HBV DNA a quantitative marker of this replicative phase, during which all three forms of HBV circulate, including intact virions. Over time, the relatively replicative phase of chronic HBV infection gives way to a relatively *nonreplicative phase*. This occurs at a rate of ~10% per year and is accompanied by seroconversion from HBeAg to anti-HBe. In many cases, this seroconversion coincides with a transient, usually mild, acute hepatitis-like elevation in aminotransferase activity, believed to reflect cell-mediated immune clearance of virus-infected hepatocytes. In the nonreplicative phase of chronic infection, when HBV DNA is demonstrable in hepatocyte nuclei, it tends to be integrated into the host genome. In this phase, only spherical and tubular forms of HBV, *not intact virions*, circulate, and liver injury tends to subside. Most such patients would be characterized as *inactive HBV carriers*. In reality, the designations *replicative* and *nonreplicative* are only relative; even in the so-called nonreplicative phase, HBV replication can be detected at levels of approximately $\leq 10^3$ virions/mL with highly sensitive amplification probes such as the polymerase chain reaction (PCR); below this replication threshold, liver injury and infectivity of HBV are limited to negligible. Still, the distinctions are pathophysiologically and clinically meaningful. Occasionally, nonreplicative HBV infection converts back to replicative infection. Such spontaneous reactivations are accompanied by reexpression of HBeAg and HBV DNA, and sometimes of IgM anti-HBc, as well as by exacerbations of liver injury. Because high-titer IgM anti-HBc can reappear during acute exacerbations of chronic hepatitis B, relying on IgM anti-HBc versus IgG anti-HBc to distinguish between acute and chronic hepatitis B infection, respectively, may not always be reliable; in such cases, patient history and additional follow-up monitoring over time are invaluable in helping to distinguish de novo acute hepatitis B infection from acute exacerbation of chronic hepatitis B infection.

MOLECULAR VARIANTS Variation occurs throughout the HBV genome, and clinical isolates of HBV that do not express typical viral proteins have been attributed to mutations in individual or even multiple gene locations. For example, variants have been described that lack nucleocapsid proteins (commonly), envelope proteins (very rarely), or both. Two categories of naturally occurring HBV variants have attracted the most attention. One of these was identified initially in Mediterranean countries among patients with severe chronic HBV infection and detectable HBV DNA, but with anti-HBe instead of HBeAg. These patients were found to be infected with an HBV mutant that contained an alteration in the precore region rendering the virus incapable of encoding HBeAg. Although several potential mutation sites exist in the pre-C region, the region of the C gene necessary for the expression of HBeAg (see "Virology and Etiology"), the most commonly encountered in such patients is a single base substitution, from G to A in the second to last codon of the pre-C gene at nucleotide 1896. This substitution results in the replacement of the TGG tryptophan codon by a stop codon (TAG), which prevents the translation of HBeAg. Another mutation, in the core-promoter region, prevents transcription of the coding region for HBeAg and yields an HBeAg-negative phenotype. Patients with such mutations in the precore region and who are unable to secrete HBeAg may have severe liver disease that progresses more rapidly to cirrhosis, or alternatively, they are identified clinically later in the course of the natural history of chronic hepatitis B, when the disease is more advanced. Both "wild-type" HBV and precore-mutant HBV can coexist in the same patient, or mutant HBV may arise late during wild-type HBV infection. In addition, clusters of fulminant hepatitis B in Israel and Japan were attributed to common-source infection with a precore mutant. Fulminant hepatitis B in North America and western Europe, however, occurs in patients infected with wild-type HBV, in the absence of precore mutants, and both precore mutants and other mutations throughout the HBV genome occur commonly, even in patients with typical, self-limited, milder forms of HBV infection. HBeAg-negative chronic hepatitis with mutations in the precore region is now the most frequently encountered form of hepatitis B in Mediterranean countries and in Europe. In the United States, where HBV genotype A (less prone to G1896A mutation) is prevalent, precore-mutant HBV is much less common; however, as a result of immigration from Asia and Europe, the proportion of HBeAg-negative hepatitis B–infected individuals has increased in the United States, and they now represent ~30–40% of patients with chronic hepatitis B. Characteristic of such HBeAg-negative chronic hepatitis B are lower levels of HBV DNA (usually $\leq 10^5$ IU/mL) and one of several patterns of aminotransferase activity—persistent elevations, periodic fluctuations above the normal range, and periodic fluctuations between the normal and elevated range.

The second important category of HBV mutants consists of *escape mutants*, in which a single amino acid substitution, from glycine to arginine, occurs at position 145 of the immunodominant *a* determinant common to all HBsAg subtypes. This HBsAg alteration leads to a critical conformational change that results in a loss of neutralizing activity by anti-HBs. This specific HBV/*a* mutant has been observed in two situations, active and passive immunization, in which humoral immunologic pressure may favor evolutionary change ("escape") in the virus—in a small number of hepatitis B vaccine recipients who acquired HBV infection despite the prior appearance of neutralizing anti-HBs and in HBV-infected liver transplant recipients treated with a high-potency human monoclonal anti-HBs preparation. Although such mutants have not been recognized frequently, their existence raises a concern that may complicate vaccination strategies and serologic diagnosis.

Different types of mutations emerge during antiviral therapy of chronic hepatitis B with nucleoside analogues; such "YMDD" and similar mutations in the polymerase motif of HBV are described in Chap. 334.

EXTRAHEPATIC SITES Hepatitis B antigens and HBV DNA have been identified in extrahepatic sites, including the lymph nodes, bone marrow, circulating lymphocytes, spleen, and pancreas. Although the virus does not appear to be associated with tissue injury in any of these extrahepatic sites, its presence in these "remote" reservoirs has been invoked (but is not necessary) to explain the recurrence of HBV infection after orthotopic liver transplantation. The clinical relevance of such extrahepatic HBV is limited.

Hepatitis D

The delta hepatitis agent, or HDV, the only member of the genus *Deltavirus*, is a defective RNA virus that co-infects with and requires the helper function of HBV (or other hepadnaviruses) for its replication and expression. Slightly smaller than HBV, HDV is a formalin-sensitive, 35- to 37-nm virus with a hybrid structure. Its nucleocapsid expresses HDV antigen (HDAg), which bears no antigenic homology with any of the HBV antigens, and contains the virus genome. The HDV core is "encapsidated" by an outer envelope of HBsAg, indistinguishable from that of HBV except in its relative compositions of major, middle, and large HBsAg component proteins. The genome is a small, 1700-nucleotide, circular, single-strand RNA of negative polarity that is nonhomologous with HBV DNA (except for a small area of the polymerase gene) but that has features and the rolling circle model of replication common to genomes of plant satellite viruses or viroids. HDV RNA contains many areas of internal complementarity; therefore, it can fold on itself by internal base pairing to form an unusual, very stable, rodlike structure that contains a very stable, self-cleaving and self-ligating ribozyme. HDV RNA requires host RNA polymerase II for its replication in the hepatocyte nucleus via RNA-directed RNA synthesis by transcription of genomic RNA to a complementary antigenomic (plus strand) RNA; the antigenomic RNA, in turn, serves as a template for subsequent genomic RNA synthesis effected by host RNA polymerase I. HDV RNA has only one open reading frame, and HDAg, a product of the antigenomic strand, is the only known HDV protein; HDAg exists in two forms: a small, 195-amino-acid species, which plays a role in facilitating HDV RNA replication, and a large, 214-amino-acid species, which appears to suppress replication but is required for assembly of the antigen into virions. HDV antigens have been shown to bind directly to RNA polymerase II,

resulting in stimulation of transcription. Although complete hepatitis D virions and liver injury require the cooperative helper function of HBV, intracellular replication of HDV RNA can occur without HBV. Genomic heterogeneity among HDV isolates has been described; however, pathophysiologic and clinical consequences of this genetic diversity have not been recognized. The clinical spectrum of hepatitis D is common to all eight genotypes identified, the predominant of which is genotype 1.

HDV can either infect a person simultaneously with HBV (*co-infection*) or superinfect a person already infected with HBV (*superinfection*); when HDV infection is transmitted from a donor with one HBsAg subtype to an HBsAg-positive recipient with a different subtype, HDV assumes the HBsAg subtype of the recipient, rather than the donor. Because HDV relies absolutely on HBV, the duration of HDV infection is determined by the duration of (and cannot outlast) HBV infection. HDV replication tends to suppress HBV replication; therefore, patients with hepatitis D tend to have lower levels of HBV replication. HDV antigen is expressed primarily in hepatocyte nuclei and is occasionally detectable in serum. During acute HDV infection, anti-HDV of the IgM class predominates, and 30–40 days may elapse after symptoms appear before anti-HDV can be detected. In self-limited infection, anti-HDV is low-titer and transient, rarely remaining detectable beyond the clearance of HBsAg and HDV antigen. In chronic HDV infection, anti-HDV circulates in high titer, and both IgM and IgG anti-HDV can be detected. HDV antigen in the liver and HDV RNA in serum and liver can be detected during HDV replication.

Hepatitis C Hepatitis C virus, which, before its identification was labeled "non-A, non-B hepatitis," is a linear, single-strand, positive-sense, 9600-nucleotide RNA virus, the genome of which is similar in organization to that of flaviviruses and pestiviruses; HCV is the only member of the genus *Hepacivirus* in the family Flaviviridae. The HCV genome contains a single, large open reading frame (ORF) (gene) that codes for a virus polyprotein of ~3000 amino acids, which is cleaved after translation to yield 10 viral proteins. The 5′ end of the genome consists of an untranslated region (containing an internal ribosomal entry site [IRES]) adjacent to the genes for three structural proteins, the nucleocapsid core protein, C, and two envelope glycoproteins, E1 and E2. The 5′ untranslated region and core gene are highly conserved among genotypes, but the envelope proteins are coded for by the hypervariable region, which varies from isolate to isolate and may allow the virus to evade host immunologic containment directed at accessible virus-envelope proteins. The 3′ end of the genome also includes an untranslated region and contains the genes for seven nonstructural (NS) proteins: p7, NS2, NS3, NS4A, NS4B, NS5A, and NS5B. p7 is a membrane ion channel protein necessary for efficient assembly and release of HCV. The NS2 cysteine protease cleaves NS3 from NS2, and the NS3-4A serine protease cleaves all the downstream proteins from the polyprotein. Important NS proteins involved in virus replication include the NS3 helicase; NS3-4A serine protease; the multifunctional membrane-associated phosphoprotein NS5A, an essential component of the viral replication membranous web (along with NS4B); and the NS5B RNA-dependent RNA polymerase **(Fig. 332-6)**. Because HCV does not replicate via a DNA intermediate, it does not integrate into the host genome. Because HCV tends to circulate in relatively low titer, 10^3–10^7 virions/mL, visualization of the 50- to 80-nm virus particles remains difficult. Still, the replication rate of HCV is very high, 10^{12} virions per day; its half-life is 2.7 h. The chimpanzee is a helpful but cumbersome animal model. Although a robust, reproducible, small animal model is lacking, HCV replication has been documented in an immunodeficient mouse model containing explants of human liver and in transgenic mouse and rat models. Although in vitro replication is difficult, replicons in hepatocellular carcinoma–derived cell lines support replication of genetically manipulated, truncated, or full-length HCV RNA (but not intact virions); infectious pseudotyped retroviral HCV particles have been shown to yield functioning envelope proteins. In 2005, complete replication of HCV and intact 55-nm virions were described in cell culture systems. HCV entry into the hepatocyte occurs via the nonliver-specific CD81 receptor and the liver-specific tight junction protein claudin-1. A growing list of additional host receptors to which HCV binds on cell entry includes occludin, low-density lipoprotein receptors, glycosaminoglycans, scavenger receptor B1, and epidermal growth factor receptor, among others. Relying on the same assembly and secretion pathway as low-density and very-low-density lipoproteins, HCV is a lipoviroparticle and masquerades as a lipoprotein, which may limit its visibility to the adaptive immune system and explain its ability to evade immune containment and clearance. After viral entry and uncoating, translation is initiated by the IRES on the endoplasmic reticulum membrane, and the HCV polyprotein is cleaved during translation and posttranslationally by host cellular proteases as well as HCV NS2-3 and NS3-4A proteases. Host cofactors involved in HCV replication include cyclophilin A, which binds to NS5A and yields conformational changes required for viral replication, and liver-specific host microRNA miR-122.

At least six distinct major genotypes (and a minor genotype 7), as well as >50 subtypes within genotypes, of HCV have been identified by nucleotide sequencing. Genotypes differ from one another in sequence homology by ≥30%, and subtypes differ by ~20%. Because divergence of HCV isolates within a genotype or subtype and within the same host may vary insufficiently to define a distinct genotype, these intragenotypic differences are referred to as *quasispecies* and differ in sequence homology by only a few percent. The genotypic and quasispecies diversity of HCV, resulting from its high mutation rate, interferes with effective humoral immunity. Neutralizing antibodies to HCV have been demonstrated, but they tend to be short-lived, and HCV infection does not induce lasting immunity against reinfection with different virus isolates or even the same virus isolate. Thus, neither *heterologous* nor *homologous* immunity appears to develop commonly after acute HCV infection. Some HCV genotypes are distributed worldwide, whereas others are more geographically confined (see "Epidemiology and Global Features"). In addition, differences exist among genotypes in responsiveness to antiviral therapy but not in pathogenicity or clinical progression (except for genotype 3, in which hepatic steatosis and clinical progression are more likely).

Currently available, third-generation immunoassays, which incorporate proteins from the core, NS3, and NS5 regions, detect anti-HCV antibodies during acute infection. The most sensitive indicator of HCV infection is the presence of HCV RNA, which requires molecular amplification by PCR or transcription-mediated amplification (TMA)

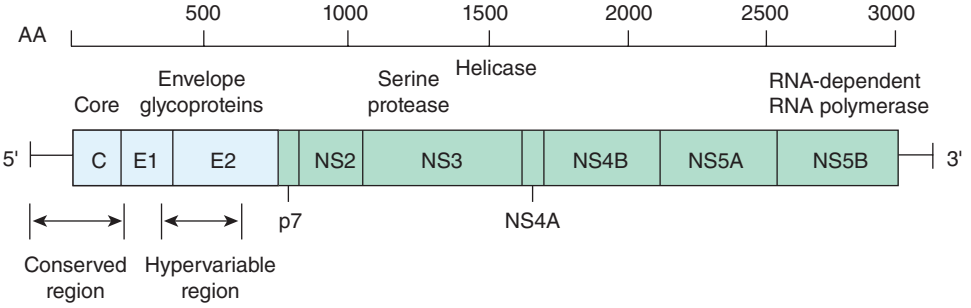

FIGURE 332-6 Organization of the hepatitis C virus genome and its associated, 3000-amino-acid (AA) proteins. The three structural genes at the 5′ end are the core region, C, which codes for the nucleocapsid, and the envelope regions, E1 and E2, which code for envelope glycoproteins. The 5′ untranslated region and the C region are highly conserved among isolates, whereas the envelope domain E2 contains the hypervariable region. At the 3′ end are seven nonstructural (NS) regions—p7, a membrane protein adjacent to the structural proteins that appears to function as an ion channel; NS2, which codes for a cysteine protease; NS3, which codes for a serine protease and an RNA helicase; NS4 and NS4B; NS5A, a multifunctional membrane-associated phosphoprotein, an essential component of the viral replication membranous web; and NS5B, which codes for an RNA-dependent RNA polymerase. After translation of the entire polyprotein, individual proteins are cleaved by both host and viral proteases.

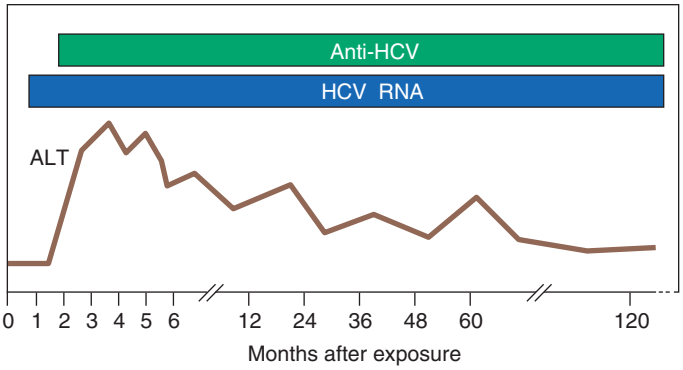

FIGURE 332-7 Scheme of typical laboratory features during acute hepatitis C progressing to chronicity. Hepatitis C virus (HCV) RNA is the first detectable event, preceding alanine aminotransferase (ALT) elevation and the appearance of anti-HCV.

(Fig. 332-7). To allow standardization of the quantification of HCV RNA among laboratories and commercial assays, HCV RNA is reported as international units (IUs) per milliliter; quantitative assays with a broad dynamic range are available that allow detection of HCV RNA with a sensitivity as low as 5 IU/mL. HCV RNA can be detected within a few days of exposure to HCV—well before the appearance of anti-HCV—and tends to persist for the duration of HCV infection. Application of sensitive molecular probes for HCV RNA has revealed the presence of replicative HCV in peripheral blood lymphocytes of infected persons; however, as is the case for HBV in lymphocytes, the clinical relevance of HCV lymphocyte infection is not known.

Hepatitis E Previously labeled *epidemic* or *enterically transmitted non-A, non-B hepatitis*, HEV is an enterically transmitted virus that causes clinically apparent hepatitis primarily in India, Asia, Africa, and Central America; in those geographic areas, HEV is the most common cause of acute hepatitis; one-third of the global population appears to have been infected. This agent, with epidemiologic features resembling those of hepatitis A, is a 27- to 34-nm, nonenveloped, heat-stable, HAV-like virus with a 7200-nucleotide, single-strand, positive-sense RNA genome. HEV has three overlapping ORFs (genes), the largest of which, *ORF1*, encodes nonstructural proteins involved in virus replication (viral replicase). A middle-sized gene, *ORF2*, encodes the nucleocapsid protein, the major structural protein, and the smallest, *ORF3*, encodes a small structural protein involved in virus particle secretion. All HEV isolates appear to belong to a single serotype, despite genomic heterogeneity of up to 25% and the existence of five genotypes, only four of which have been detected in humans; genotypes 1 and 2 (common in developing countries) appear to be more virulent, whereas genotypes 3 (the most common in the United States and Europe) and 4 (seen in China) are more attenuated and account for subclinical infections. Contributing to the perpetuation of this virus are animal reservoirs, most notably in swine but also in camels, deer, rats, and rabbits, among others. No genomic or antigenic homology, however, exists between HEV and HAV or other picornaviruses; and HEV, although resembling caliciviruses, is sufficiently distinct from any known agent to merit its own classification as a unique genus, *Hepevirus*, within the family Hepeviridae. The virus has been detected in stool, bile, and liver, and is excreted in the stool during the late incubation period. Both IgM anti-HEV during early acute infection and IgG anti-HEV predominating after the first 3 months can be detected. The presence of HEV RNA in serum and stool accompanies acute infection; viremia resolves as clinical-biochemical recovery ensues, while HEV RNA in stool may outlast viremia by several weeks. Currently, availability and reliability of serologic/virologic testing for HEV infection is limited—and not FDA-approved or licensed—but can be done in specialized laboratories (e.g., the Centers for Disease Control and Prevention).

PATHOGENESIS

Under ordinary circumstances, none of the hepatitis viruses is known to be directly cytopathic to hepatocytes. Evidence suggests that the clinical manifestations and outcomes after acute liver injury associated with viral hepatitis are determined by the immunologic responses of the host. Among the viral hepatitides, the immunopathogenesis of hepatitis B and C has been studied most extensively.

Hepatitis B For HBV, the existence of inactive hepatitis B carriers with normal liver histology and function suggests that the virus is not directly cytopathic. The fact that patients with defects in cellular immune competence are more likely to remain chronically infected rather than to clear HBV supports the role of cellular immune responses in the pathogenesis of hepatitis B–related liver injury. The model that has the most experimental support involves cytolytic T cells sensitized specifically to recognize host and hepatitis B viral antigens on the liver cell surface. Nucleocapsid proteins (HBcAg and possibly HBeAg), present on the cell membrane in minute quantities, are the viral target antigens that, with host antigens, invite cytolytic T cells to destroy HBV-infected hepatocytes. Differences in the robustness and broad polyclonality of CD8+ cytolytic T cell responsiveness; in the level of HBV-specific helper CD4+ T cells; in attenuation, depletion, and exhaustion of virus-specific T cells; in viral T cell epitope escape mutations that allow the virus to evade T cell containment; and in the elaboration of antiviral cytokines by T cells have been invoked to explain differences in outcomes between those who recover after acute hepatitis and those who progress to chronic hepatitis, or between those with mild and those with severe (fulminant) acute HBV infection.

Although a robust cytolytic T cell response occurs and eliminates virus-infected liver cells during acute hepatitis B, >90% of HBV DNA has been found in experimentally infected chimpanzees to disappear from the liver and blood before maximal T cell infiltration of the liver and before most of the biochemical and histologic evidence of liver injury. This observation suggests that components of the innate immune system and inflammatory cytokines, independent of cytopathic antiviral mechanisms, participate in the early immune response to HBV infection; this effect has been shown to represent elimination of HBV replicative intermediates from the cytoplasm and covalently closed circular viral DNA from the nucleus of infected hepatocytes. In turn, the innate immune response to HBV infection is mediated largely by natural killer (NK) cell cytotoxicity, activated by immunosuppressive cytokines (e.g., interleukin [IL] 10 and transforming growth factor [TGF] β), reduced signals from inhibitory receptor expression (e.g., major histocompatibility complex), or increased signals from activating receptor expression on infected hepatocytes. In addition, NK cells reduce helper CD4+ cells, which results in reduced CD8+ cells and exhaustion of the virus-specific T cell response to HBV infection. Ultimately, HBV-HLA–specific cytolytic T cell responses of the adaptive immune system are felt to be responsible for recovery from HBV infection.

Debate continues over the relative importance of viral and host factors in the pathogenesis of HBV-associated liver injury and its outcome. As noted above, precore genetic mutants of HBV have been associated with the more severe outcomes of HBV infection (severe chronic and fulminant hepatitis), suggesting that, under certain circumstances, relative pathogenicity is a property of the virus, not the host. The facts that concomitant HDV and HBV infections are associated with more severe liver injury than HBV infection alone and that cells transfected in vitro with the gene for HDV antigen express HDV antigen and then become necrotic in the absence of any immunologic influences are also consistent with a viral effect on pathogenicity. Similarly, in patients who undergo liver transplantation for end-stage chronic hepatitis B, occasionally, rapidly progressive liver injury appears in the new liver. This clinical pattern is associated with an unusual histologic pattern in the new liver, *fibrosing cholestatic hepatitis*, which, ultrastructurally, appears to represent a choking of the cell with overwhelming quantities of HBsAg. This observation suggests that, under the influence of the potent immunosuppressive agents required to prevent allograft rejection, HBV may have a direct cytopathic effect on liver cells, independent of the immune system.

Although the precise mechanism of liver injury in HBV infection remains elusive, studies of nucleocapsid proteins have shed light on

the profound immunologic tolerance to HBV of babies born to mothers with highly replicative (HBeAg-positive), chronic HBV infection. In HBeAg-expressing transgenic mice, in utero exposure to HBeAg, which is sufficiently small to traverse the placenta, induces T cell tolerance to both nucleocapsid proteins. This, in turn, may explain why, when infection occurs so early in life, immunologic clearance does not occur, and protracted, lifelong infection ensues. An alternative explanation proposed to explain why robust liver injury does not accompany neonatal HBV infection but predisposes to chronic infection is defective priming of HBV-specific T cells during in utero exposure to HBV.

An important distinction should be drawn between HBV infection acquired at birth, common in endemic areas, such as East Asia, and infection acquired in adulthood, common in the West. Infection in the neonatal period is associated with the acquisition of what appears to be a high level of immunologic tolerance to HBV and absence of an acute hepatitis illness, but the almost invariable establishment of chronic, often lifelong infection. Neonatally acquired HBV infection can culminate decades later in cirrhosis and hepatocellular carcinoma (see "Complications and Sequelae"). In contrast, when HBV infection is acquired during adolescence or early adulthood, the host immune response to HBV-infected hepatocytes tends to be robust, an acute hepatitis-like illness is the rule, and failure to recover is the exception. After adulthood-acquired infection, chronicity is uncommon, and the risk of hepatocellular carcinoma is very low. Based on these observations, some authorities categorize HBV infection into an "immunotolerant" phase, an "immunoreactive" phase, and an "inactive" phase. This somewhat simplistic formulation does not apply at all to the typical adult in the West with self-limited acute hepatitis B, in whom no period of immunologic tolerance occurs. Even among those with neonatally acquired HBV infection, in whom immunologic tolerance appears to be established definitively, immunologic responses to HBV infection have been demonstrated, and intermittent bursts of hepatic necroinflammatory activity punctuate the early decades of life during which liver injury appears to be quiescent (labeled by some as the "immunotolerant" phase; however, it more accurately is a period of dissociation between high-level HBV replication and a paucity of inflammatory liver injury). In addition, even when clinically apparent liver injury and progressive fibrosis emerge during later decades (the so-called immunoreactive, or immunointolerant, phase), the level of immunologic tolerance to HBV remains substantial. More accurately, in patients with neonatally acquired HBV infection, a dynamic equilibrium exists between tolerance and intolerance, the outcome of which determines the clinical expression of chronic infection. Persons infected as neonates tend to have a relatively higher level of immunologic tolerance (high replication, low necroinflammatory activity) during the early decades of life and a relatively lower level (but only rarely a loss) of tolerance (and necroinflammatory activity reflecting the level of virus replication) in the later decades of life.

Hepatitis C Cell-mediated immune responses and elaboration by T cells of antiviral cytokines contribute to the multicellular innate and adaptive immune responses involved in the containment of infection and pathogenesis of liver injury associated with hepatitis C. The fact that HCV is so efficient in evading these immune mechanisms is a testament to its highly evolved ability to disrupt host immune responses at multiple levels. After exposure to HCV, the host cell identifies viral product motifs (pattern recognition receptors) that distinguish the virus from "self," resulting in the elaboration of interferons and other cytokines that result in activation of innate and adaptive immune responses. Intrahepatic HLA class I–restricted cytolytic T cells directed at nucleocapsid, envelope, and nonstructural viral protein antigens have been demonstrated in patients with chronic hepatitis C; however, such virus-specific cytolytic T cell responses do not correlate adequately with the degree of liver injury or with recovery. Yet, a consensus has emerged supporting a role in the pathogenesis of HCV-associated liver injury of virus-activated CD4+ helper T cells that stimulate, via the cytokines they elaborate, HCV-specific CD8+ cytotoxic T cells. These responses appear to be more robust (higher in number, more diverse in viral antigen specificity, more functionally effective, and more long lasting) in those who recover from HCV infection than in those who have chronic infection. Contributing to chronic infection are a CD4+ proliferative defect that results in rapid contraction of CD4+ responses, mutations in CD8+ T cell–targeted viral epitopes that allow HCV to escape immune-mediated clearance, and upregulation of inhibitory receptors on functionally impaired, exhausted T cells. Although attention has focused on adaptive immunity, HCV proteins have been shown to interfere with innate immunity by resulting in blocking of type 1 interferon responses and inhibition of interferon signaling and effector molecules in the interferon signaling cascade. Several HLA alleles have been linked with self-limited hepatitis C, the most convincing of which is the CC haplotype of the *IL28B* gene, which codes for interferon λ3, a component of innate immune antiviral defense. The *IL28B* association is even stronger when combined with HLA class II *DQB1*03:01*. The link between non-CC *IL28B* polymorphisms and failure to clear HCV infection has been explained by a chromosome 19q13.13 frameshift variant upstream of *IL28B*, the ΔG polymorphism of which creates an ORF in a novel interferon gene (*IFN-λ4*) associated with impaired HCV clearance. Also shown to contribute to limiting HCV infection are NK cells of the innate immune system that function when HLA class I molecules required for successful adaptive immunity are underexpressed. Both peripheral cytotoxicity and intrahepatic NK cell cytotoxicity are dysfunctional in persistent HCV infection. Adding to the complexity of the immune response, HCV core, NS4B, and NS5B have been shown to suppress the immunoregulatory nuclear factor (NF)-κB pathway, resulting in reduced antiapoptotic proteins and a resultant increased vulnerability to tumor necrosis factor (TNF) α–mediated cell death. Patients with hepatitis C and unfavorable (non-CC, associated with reduced HCV clearance) *IL28B* alleles have been shown to have depressed NK cell/innate immune function. Of note, the emergence of substantial viral quasispecies diversity and HCV sequence variation allow the virus to evade attempts by the host to contain HCV infection by both humoral and cellular immunity.

Finally, cross-reactivity between viral antigens (HCV NS3 and NS5A) and host autoantigens (cytochrome P450 2D6) has been invoked to explain the association between hepatitis C and a subset of patients with autoimmune hepatitis and antibodies to liver-kidney microsomal (LKM) antigen (anti-LKM) **(Chap. 334)**.

EXTRAHEPATIC MANIFESTATIONS

Immune complex–mediated tissue damage appears to play a pathogenetic role in the extrahepatic manifestations of acute hepatitis B. The occasional prodromal serum sickness–like syndrome observed in acute hepatitis B appears to be related to the deposition in tissue blood vessel walls of HBsAg-anti-HBs circulating immune complexes, leading to activation of the complement system and depressed serum complement levels.

In patients with chronic hepatitis B, other types of immune-complex disease may be seen. Glomerulonephritis with the nephrotic syndrome is observed occasionally; HBsAg, immunoglobulin, and C3 deposition has been found in the glomerular basement membrane. Whereas generalized vasculitis (polyarteritis nodosa) develops in considerably <1% of patients with chronic HBV infection, 20–30% of patients with polyarteritis nodosa have HBsAg in serum **(Chap. 356)**. In these patients, the affected small- and medium-size arterioles contain HBsAg, immunoglobulins, and complement components. Another extrahepatic manifestation of viral hepatitis, essential mixed cryoglobulinemia (EMC), was reported initially to be associated with hepatitis B. The disorder is characterized clinically by arthritis, cutaneous vasculitis (palpable purpura), and, occasionally, glomerulonephritis and serologically by the presence of circulating cryoprecipitable immune complexes of more than one immunoglobulin class **(Chaps. 308 and 356)**. Many patients with this syndrome have chronic liver disease, but the association with HBV infection is limited; instead, a substantial proportion has chronic HCV infection, with circulating immune complexes containing HCV RNA. Immune-complex glomerulonephritis is another recognized extrahepatic manifestation of chronic hepatitis C. Immune-complex disorders have been linked, albeit rarely, with both hepatitis A and E. In hepatitis E,

rare neurologic complications have been postulated to result from both immunologic mechanisms and/or direct CNS infection with the virus.

PATHOLOGY

The typical morphologic lesions of all types of viral hepatitis are similar and consist of panlobular infiltration with mononuclear cells, hepatic cell necrosis, hyperplasia of Kupffer cells, and variable degrees of cholestasis. Hepatic cell regeneration is present, as evidenced by numerous mitotic figures, multinucleated cells, and "rosette" or "pseudoacinar" formation. The mononuclear infiltration consists primarily of small lymphocytes, although plasma cells and eosinophils occasionally are present. Liver cell damage consists of hepatic cell degeneration and necrosis, cell dropout, ballooning of cells, and acidophilic degeneration of hepatocytes (forming so-called Councilman or apoptotic bodies). Large hepatocytes with a ground-glass appearance of the cytoplasm may be seen in chronic but not in acute HBV infection; these cells contain HBsAg and can be identified histochemically with orcein or aldehyde fuchsin. In uncomplicated viral hepatitis, the reticulin framework is preserved.

In hepatitis C, the histologic lesion is often remarkable for a relative paucity of inflammation, a marked increase in activation of sinusoidal lining cells, lymphoid aggregates, the presence of fat (more frequent in genotype 3 and linked to increased fibrosis), and, occasionally, bile duct lesions in which biliary epithelial cells appear to be piled up without interruption of the basement membrane. Occasionally, microvesicular steatosis occurs in hepatitis D. In hepatitis E, a common histologic feature is marked cholestasis. A cholestatic variant of slowly resolving acute hepatitis A also has been described.

A more severe histologic lesion, *bridging hepatic necrosis*, also termed *subacute* or *confluent necrosis* or *interface hepatitis*, is observed occasionally in acute hepatitis. "Bridging" between lobules results from large areas of hepatic cell dropout, with collapse of the reticulin framework. Characteristically, the bridge consists of condensed reticulum, inflammatory debris, and degenerating liver cells that span adjacent portal areas, portal to central veins, or central vein to central vein. This lesion had been thought to have prognostic significance; in many of the originally described patients with this lesion, a subacute course terminated in death within several weeks to months, or severe chronic hepatitis and cirrhosis developed; however, the association between bridging necrosis and a poor prognosis in patients with acute hepatitis has not been upheld. Therefore, although demonstration of this lesion in patients with chronic hepatitis has prognostic significance **(Chap. 334)**, its demonstration during acute hepatitis is less meaningful, and liver biopsies to identify this lesion are no longer undertaken routinely in patients with acute hepatitis. In *massive hepatic necrosis* (fulminant hepatitis, "acute yellow atrophy"), the striking feature at postmortem examination is the finding of a small, shrunken, soft liver. Histologic examination reveals massive necrosis and dropout of liver cells of most lobules with extensive collapse and condensation of the reticulin framework. When histologic documentation is required in the management of fulminant or very severe hepatitis, a biopsy can be done by the angiographically guided transjugular route, which permits the performance of this invasive procedure in the presence of severe coagulopathy.

Immunohistochemical and electron-microscopic studies have localized HBsAg to the cytoplasm and plasma membrane of infected liver cells. In contrast, HBcAg predominates in the nucleus, but, occasionally, scant amounts are also seen in the cytoplasm and on the cell membrane. HDV antigen is localized to the hepatocyte nucleus, whereas HAV, HCV, and HEV antigens are localized to the cytoplasm.

EPIDEMIOLOGY AND GLOBAL FEATURES

Before the availability of serologic tests for hepatitis viruses, all viral hepatitis cases were labeled either as "infectious" or "serum" hepatitis. Modes of transmission overlap, however, and *a clear distinction among the different types of viral hepatitis cannot be made solely on the basis of clinical or epidemiologic features* **(Table 332-2)**. The most accurate means to distinguish the various types of viral hepatitis involves specific serologic testing.

Hepatitis A *This agent is transmitted almost exclusively by the fecal-oral route*. Person-to-person spread of HAV is enhanced by poor personal hygiene and overcrowding; large outbreaks as well as sporadic cases have been traced to contaminated food, water, milk, frozen raspberries and strawberries, green onions imported from Mexico, and shellfish (e.g., scallops imported from the Philippines used to make sushi, the culprit identified in a 2016 Hawaiian outbreak). Intrafamily and intrainstitutional spreads are also common. Early epidemiologic observations supported a predilection for hepatitis A to occur in late fall and early winter. In temperate zones, epidemic waves have been recorded every 5–20 years as new segments of nonimmune population appeared; however, in developed countries, the incidence of hepatitis A has been declining, presumably as a function of improved sanitation, and these cyclic patterns are no longer observed. No HAV carrier state has been identified after acute hepatitis A; perpetuation of the virus in nature depends presumably on nonepidemic, inapparent subclinical infection, ingestion of contaminated food or water in, or imported from, endemic areas, and/or contamination linked to environmental reservoirs.

In the general population, anti-HAV, a marker for previous HAV infection, increases in prevalence as a function of increasing age and of decreasing socioeconomic status. In the 1970s, serologic evidence of prior hepatitis A infection occurred in ~40% of urban populations in the United States, most of whose members never recalled having had a symptomatic case of hepatitis. In subsequent decades, however, the prevalence of anti-HAV has been declining in the United States. In developing countries, exposure, infection, and subsequent immunity are almost universal in childhood. As the frequency of subclinical childhood infections declines in developed countries, a susceptible cohort of adults emerges. Hepatitis A tends to be more symptomatic in adults; therefore, paradoxically, as the frequency of HAV infection declines, the likelihood of clinically apparent, even severe, HAV illnesses increases in the susceptible adult population. Travel to endemic areas is a common source of infection for adults from nonendemic areas. More recently recognized epidemiologic foci of HAV infection include child care centers, neonatal intensive care units, promiscuous men who have sex with men, injection drug users, and unvaccinated close contacts of newly arrived international adopted children, most of whom emanate from countries with intermediate-to-high hepatitis A endemicity. Although hepatitis A is rarely bloodborne, several outbreaks have been recognized in recipients of clotting-factor concentrates. In the United States, the introduction of hepatitis A vaccination programs among children from high-incidence states has resulted in a >70% reduction in the annual incidence of new HAV infections and has shifted the burden of new infections from children to adults. In the 2007–2012 U.S. Public Health Service National Health and Nutrition Examination Survey (NHANES), the prevalence of anti-HAV in the U.S. population aged ≥20 years had declined to 24.2% from the 29.5% measured in NHANES 1999–2006. While universal childhood vaccination accounted for a high prevalence of vaccine-induced immunity in children aged 2–19 years, the lowest age-specific prevalence of anti-HAV (16.1–17.6%) occurred in adults in the fourth and fifth decades, respectively (aged 30–49 years). This is a subgroup of the population who remain susceptible to acute hepatitis A acquired during travel to endemic areas and from contaminated foods, especially those imported from endemic countries.

Hepatitis B Percutaneous inoculation has long been recognized as a major route of hepatitis B transmission, but the outmoded designation "serum hepatitis" is an inaccurate label for the epidemiologic spectrum of HBV infection. As detailed below, most of the hepatitis transmitted by blood transfusion is not caused by HBV; moreover, in approximately two-thirds of patients with acute type B hepatitis, no history of an identifiable percutaneous exposure can be elicited. We now recognize that many cases of hepatitis B result from less obvious modes of nonpercutaneous or covert percutaneous transmission. HBsAg has been identified in almost every body fluid from infected persons, and at least some of these body fluids—most notably semen and saliva—are infectious, albeit less so than serum, when administered percutaneously or nonpercutaneously to experimental animals. Among the nonpercutaneous

TABLE 332-2 Clinical and Epidemiologic Features of Viral Hepatitis

FEATURE	HAV	HBV	HCV	HDV	HEV
Incubation (days)	15–45, mean 30	30–180, mean 60–90	15–160, mean 50	30–180, mean 60–90	14–60, mean 40
Onset	Acute	Insidious or acute	Insidious or acute	Insidious or acute	Acute
Age preference	Children, young adults	Young adults (sexual and percutaneous), babies, toddlers	Any age, but more common in adults	Any age (similar to HBV)	Epidemic cases: young adults (20–40 years); sporadic cases: older adults (>60)
Transmission					
Fecal-oral	+++	–	–	–	+++
Percutaneous	Unusual	+++	+++	+++	–
Perinatal	–	+++	±[a]	+	–
Sexual	±	++	±[a]	++	–
Clinical					
Severity	Mild	Occasionally severe	Moderate	Occasionally severe	Mild
Fulminant	0.1%	0.1–1%	0.1%	5–20%[b]	1–2%[e]
Progression to chronicity	None	Occasional (1–10%) (90% of neonates)	Common (85%)	Common[d]	None[f]
Carrier	None	0.1–30%[c]	1.5–3.2%	Variable[g]	None
Cancer	None	+ (neonatal infection)	+	±	None
Prognosis	Excellent	Worse with age, debility	Moderate	Acute, good Chronic, poor	Good
Prophylaxis	Ig, inactivated vaccine	HBIG, recombinant vaccine	None	HBV vaccine (none for HBV carriers)	Vaccine
Therapy	None	Interferon Lamivudine Adefovir Pegylated interferon[h] Entecavir[h] Telbivudine Tenofovir[h]	Pegylated interferon ribavirin telaprevir,[i] boceprevir,[i] simeprevir, sofosbuvir, ledipasvir, paritaprevir/ritonavir ombitasvir, dasabuvir daclatasvir, velpatasvir, grazoprevir, elbasvir	Pegylated interferon ±	None[j]

[a]Primarily with HIV co-infection and high-level viremia in index case; more likely in persons with multiple sex partners or sexually transmitted diseases; risk ~5%. [b]Up to 5% in acute HBV/HDV co-infection; up to 20% in HDV superinfection of chronic HBV infection.[c] Varies considerably throughout the world and in subpopulations within countries; see text. [d]In acute HBV/HDV co-infection, the frequency of chronicity is the same as that for HBV; in HDV superinfection, chronicity is invariable. [e]10–20% in pregnant women. [f]Except as observed in immunosuppressed liver allograft recipients or other immunosuppressed hosts. [g]Common in Mediterranean countries; rare in North America and western Europe. [h]First-line agents. [i]No longer recommended. [j]Anecdotal reports and retrospective studies suggest that pegylated interferon and/or ribavirin are effective in treating chronic hepatitis E, observed in immunocompromised persons; ribavirin monotherapy has been used successfully in acute, severe hepatitis E.

Abbreviation: HBIG, hepatitis B immunoglobulin. See text for other abbreviations.

modes of HBV transmission, oral ingestion has been documented as a potential but inefficient route of exposure. By contrast, the two nonpercutaneous routes considered to have the greatest impact are intimate (especially sexual) contact and perinatal transmission.

In sub-Saharan Africa, intimate contact among toddlers is considered instrumental in contributing to the maintenance of the high frequency of hepatitis B in the population. Perinatal transmission occurs primarily in infants born to mothers with chronic hepatitis B or (rarely) mothers with acute hepatitis B during the third trimester of pregnancy or during the early postpartum period. Perinatal transmission is uncommon in North America and western Europe but occurs with great frequency and is the most important mode of HBV perpetuation in East Asia and developing countries. Although the precise mode of perinatal transmission is unknown, and although ~10% of infections may be acquired in utero, epidemiologic evidence suggests that most infections occur approximately at the time of delivery and are not related to breast-feeding (which is not contraindicated in women with hepatitis B). The likelihood of perinatal transmission of HBV correlates with the presence of HBeAg and high-level viral replication; 90% of HBeAg-positive mothers but only 10–15% of anti-HBe-positive mothers transmit HBV infection to their offspring. In most cases, acute infection in the neonate is clinically asymptomatic, but the child is very likely to remain chronically infected.

The >350–400 million persons with chronic HBV infection in the world constitute the main reservoir of hepatitis B in human beings. Whereas serum HBsAg is infrequent (0.1–0.5%) in normal populations in the United States and western Europe, a prevalence of up to 5–20% has been found in East Asia and in some tropical countries; in persons with Down's syndrome, lepromatous leprosy, leukemia, Hodgkin's disease, or polyarteritis nodosa; in patients with chronic renal disease on hemodialysis; and in injection drug users.

Other groups with high rates of HBV infection include spouses of acutely infected persons; sexually promiscuous persons (especially promiscuous men who have sex with men); health care workers exposed to blood; persons who require repeated transfusions especially with pooled blood-product concentrates (e.g., hemophiliacs); residents and staff of custodial institutions for the developmentally handicapped; prisoners; and, to a lesser extent, family members of chronically infected patients. In volunteer blood donors, the prevalence of anti-HBs, a reflection of previous HBV infection, ranges from 5% to 10%, but the prevalence is higher in lower socioeconomic strata, older age groups, and persons—including those mentioned above—exposed to blood products. Because of highly sensitive virologic screening of donor blood, the risk of acquiring HBV infection from a blood transfusion is 1 in 230,000.

Prevalence of infection, modes of transmission, and human behavior conspire to mold geographically different epidemiologic patterns of HBV infection. In East Asia and Africa, hepatitis B, a disease of the newborn and young children, is perpetuated by a cycle of maternal-neonatal spread. In North America and western Europe, hepatitis B is primarily a disease of adolescence and early adulthood, the time of life when intimate sexual contact and recreational and occupational percutaneous exposures tend to occur. To some degree, however, this dichotomy between high-prevalence and low-prevalence geographic regions has been minimized by immigration from high-prevalence to low-prevalence areas. For example, in the United States, NHANES data from 2007 to 2012 revealed an overall prevalence of current HBV infection (detectable HBsAg) of 0.3%; however, the prevalence in Asian persons,

TABLE 332-3 High-Risk Populations for Whom HBV Infection Screening Is Recommended

Persons born in countries/regions with a high (≥8%) and intermediate (≥2%) prevalence of HBV infection including immigrants and adopted children and including persons born in the United States who were not vaccinated as infants and whose parents emigrated from areas of high HBV endemicity
Household and sexual contacts of persons with hepatitis B
Babies born to HBsAg-positive mothers
Persons who have used injection drugs
Persons with multiple sexual contacts or a history of sexually transmitted disease
Men who have sex with men
Inmates of correctional facilities
Persons with elevated alanine or aspartate aminotransferase levels
Blood/plasma/organ/tissue/semen donors
Persons with HCV or HIV infection
Hemodialysis patients
Pregnant women
Persons who are the source of blood or body fluids that would be an indication for postexposure prophylaxis (e.g., needlestick, mucosal exposure, sexual assault)
Persons who require immunosuppressive or cytotoxic therapy (including anti–tumor necrosis factor α therapy for rheumatologic or inflammatory bowel disorders)

93% of whom were foreign-born, was 10-fold higher, 3.1%, representing 50% of the U.S. national disease burden. The introduction of hepatitis B vaccine in the early 1980s and adoption of universal childhood vaccination policies in many countries resulted in a dramatic, ~90% decline in the incidence of new HBV infections in those countries as well as in the dire consequences of chronic infection, including hepatocellular carcinoma. In the United States, as demonstrated in NHANES 2007–2012, following the 1991 implementation of universal childhood vaccination, HBsAg seropositivity had declined in children aged 6–19 years to as low as 0.03%, an ~85% reduction. Populations and groups for whom HBV infection screening is recommended are listed in Table 332-3.

Hepatitis D Infection with HDV has a worldwide distribution, but two epidemiologic patterns exist. In Mediterranean countries (northern Africa, southern Europe, the Middle East), HDV infection is endemic among those with hepatitis B, and the disease is transmitted predominantly by nonpercutaneous means, especially close personal contact. In nonendemic areas, such as the United States (where hepatitis D is rare among persons with chronic hepatitis B) and northern Europe, HDV infection is confined to persons exposed frequently to blood and blood products, primarily injection drug users, (especially so in HIV-infected injection drug users) and hemophiliacs. In the United States, the prevalence of HDV infection in the national population is 0.02% (NHANES 1999–2012); however, among HBsAg-positive persons, the prevalence of HDV infection is highest in injection drug users (11%) and hemophiliacs (19%). HDV infection can be introduced into a population through drug users or by migration of persons from endemic to nonendemic areas. Thus, patterns of population migration and human behavior facilitating percutaneous contact play important roles in the introduction and amplification of HDV infection. Occasionally, the migrating epidemiology of hepatitis D is expressed in explosive outbreaks of severe hepatitis, such as those that have occurred in remote South American villages (e.g., "Lábrea fever" in the Amazon basin) as well as in urban centers in the United States. Ultimately, such outbreaks of hepatitis D—either of co-infections with acute hepatitis B or of superinfections in those already infected with HBV—may blur the distinctions between endemic and nonendemic areas. On a global scale, HDV infection declined at the end of the 1990s. Even in Italy, an HDV-endemic area, public health measures introduced to control HBV infection (e.g., mass hepatitis B vaccination) resulted during the 1990s in a 1.5%/year reduction in the prevalence of HDV infection. Still, the frequency of HDV infection during the first decade of the twenty-first century has not fallen below levels reached during the 1990s; the reservoir has been sustained by survivors infected during 1970–1980 and recent immigrants from still-endemic (e.g., Eastern Europe and Central Asia) to less-endemic countries.

Hepatitis C Routine screening of blood donors for HBsAg and the elimination of commercial blood sources in the early 1970s reduced the frequency of, but did not eliminate, transfusion-associated hepatitis. During the 1970s, the likelihood of acquiring hepatitis after transfusion of voluntarily donated, HBsAg-screened blood was ~10% per patient (up to 0.9% per unit transfused); 90–95% of these cases were classified, based on serologic exclusion of hepatitis A and B, as "non-A, non-B" hepatitis. For patients requiring transfusion of pooled products, such as clotting factor concentrates, the risk was even higher, up to 20–30%.

During the 1980s, voluntary self-exclusion of blood donors with risk factors for AIDS and then the introduction of donor screening for anti-HIV reduced further the likelihood of transfusion-associated hepatitis to <5%. During the late 1980s and early 1990s, the introduction first of "surrogate" screening tests for non-A, non-B hepatitis (alanine aminotransferase [ALT] and anti-HBc, both shown to identify blood donors with a higher likelihood of transmitting non-A, non-B hepatitis to recipients) and, subsequently, after the discovery of HCV, first-generation immunoassays for anti-HCV reduced the frequency of transfusion-associated hepatitis even further. A prospective analysis of transfusion-associated hepatitis conducted between 1986 and 1990 showed that the frequency of transfusion-associated hepatitis at one urban university hospital fell from a baseline of 3.8% per patient (0.45% per unit transfused) to 1.5% per patient (0.19% per unit) after the introduction of surrogate testing and to 0.6% per patient (0.03% per unit) after the introduction of first-generation anti-HCV assays. The introduction of second-generation anti-HCV assays reduced the frequency of transfusion-associated hepatitis C to almost imperceptible levels—1 in 100,000—and these gains were reinforced by the application of third-generation anti-HCV assays and of automated PCR testing of donated blood for HCV RNA, which has resulted in a reduction in the risk of transfusion-associated HCV infection to 1 in 2.3 million transfusions.

In addition to being transmitted by transfusion, hepatitis C can be transmitted by other percutaneous routes, such as injection drug use. In addition, this virus can be transmitted by occupational exposure to blood, and the likelihood of infection is increased in hemodialysis units. Although the frequency of transfusion-associated hepatitis C fell as a result of blood-donor screening, the overall frequency of hepatitis C remained the same until the early 1990s, when the overall frequency of reported cases fell by 80%, in parallel with a reduction in the number of new cases in injection drug users. After the exclusion of anti-HCV-positive plasma units from the donor pool, rare, sporadic instances have occurred of hepatitis C among recipients of immunoglobulin preparations for intravenous (but not intramuscular) use.

Serologic evidence for HCV infection occurs in 90% of patients with a history of transfusion-associated hepatitis (almost all occurring before 1992, when second-generation HCV screening tests were introduced); hemophiliacs and others treated with clotting factors; injection drug users; 60–70% of patients with sporadic "non-A, non-B" hepatitis who lack identifiable risk factors; 0.5% of volunteer blood donors; and, in the NHANES survey conducted in the United States between 1999 and 2002, 1.6% of the general population in the United States, which translates into 4.1 million persons (3.2 million with viremia), the majority of whom are unaware of their infections. Moreover, such population surveys do not include higher-risk groups such as incarcerated persons, homeless persons, and active injection drug users, indicating that the actual prevalence is even higher. Comparable frequencies of HCV infection occur in most countries around the world, with 170 million persons infected worldwide, but extraordinarily high prevalences of HCV infection occur in certain countries such as Egypt, where >20% of the population (as high as 50% in persons born prior to 1960) in some cities is infected. The high frequency in Egypt is attributable to contaminated equipment used for medical procedures and unsafe injection practices in the 1950s to 1980s (during a campaign to eradicate schistosomiasis with intravenous tartar emetic). In the United States,

African Americans and Mexican Americans have higher frequencies of HCV infection than whites. Data from NHANES showed that between 1988 and 1994, 30- to 40-year-old men had the highest prevalence of HCV infection; however, in a survey conducted between 1999 and 2002, the peak age decile had shifted to those age 40–49 years; an increase in hepatitis C–related mortality has paralleled this secular trend, increasing since 1995 predominantly in the 45- to 65-year age group. Thus, despite an 80% reduction in new HCV infections during the 1990s, the prevalence of HCV infection in the population was sustained by an aging cohort that had acquired their infections three to four decades earlier, during the 1960s and 1970s, as a result predominantly of self-inoculation with recreational drugs. Retrospective phylogenetic mapping of >45,000 HCV genotype 1a isolates revealed that the hepatitis C epidemic emerged in the United States between 1940 and 1965, peaking in 1950 and aligning temporally with the post-World-War-II expansion of medical procedures (including re-use of glass syringes). Thus, HCV was amplified iatrogenically not only in Egypt but also in the United States; in the United States, the seeds sewn by medical procedures in the 1950s were reaped in the 1960s and 1970s among transfusion recipients and injection drug users, even those whose drug use was confined to brief adolescent experimentation.

In NHANES 2003–2010, the prevalence of HCV infection (HCV RNA reactivity) in the United States had actually fallen to 1% (2.7 million persons) from 1.3% (3.2 million) the decade before (NHANES 1999–2002), attributable to deaths among the HCV-infected population. As death resulting from HIV infection fell after 1999, age-adjusted mortality associated with HCV infection surpassed that of HIV infection in 2007; >70% of HCV-associated deaths occurred in the "baby boomer" cohort born between 1945 and 1965. By 2012, HCV mortality had surpassed deaths from HIV, tuberculosis, hepatitis B, and 57 other notifiable infectious diseases (i.e., *all* infectious diseases) reported to the Centers for Disease Control and Prevention. In NHANES 1999–2002, compared to the 1.6% prevalence of HCV infection in the population at large, the prevalence in the 1945–1965 birth cohort was 3.2%, representing three-quarters of all infected persons. Therefore, in 2012, the Centers for Disease Control and Prevention recommended that all persons born between 1945 and 1965 be screened for hepatitis C, without ascertainment of risk, a recommendation shown to be cost-effective and predicted to identify 800,000 infected persons. Because of the availability of highly effective antiviral therapy, such screening would have the potential to avert 200,000 cases of cirrhosis and 47,000 cases of hepatocellular carcinoma and to prevent 120,000 hepatitis-related deaths; with the availability of the new generation of direct-acting antivirals (efficacy >95%, see **Chap 334**), screening baby boomers and treating those with hepatitis C have been predicted to reduce the HCV-associated disease burden by 50–70% through 2050.

Hepatitis C accounts for 40% of chronic liver disease, is the most frequent indication for liver transplantation, and is estimated to account for 8000–10,000 deaths per year in the United States. The distribution of HCV genotypes varies in different parts of the world. Worldwide, genotype 1 is the most common. In the United States, genotype 1 accounts for 70% of HCV infections, whereas genotypes 2 and 3 account for the remaining 30%; among African Americans, the frequency of genotype 1 is even higher (i.e., 90%). Genotype 4 predominates in Egypt; genotype 5 is localized to South Africa, genotype 6 to Hong Kong, and genotype 7 to Central Africa. Most asymptomatic blood donors found to have anti-HCV and ~20–30% of persons with reported cases of acute hepatitis C do not fall into a recognized risk group; however, many such blood donors do recall risk-associated behaviors when questioned carefully.

As a bloodborne infection, HCV potentially can be transmitted sexually and perinatally; however, both of these modes of transmission are inefficient for hepatitis C. Although 10–15% of patients with acute hepatitis C report having potential sexual sources of infection, most studies have failed to identify sexual transmission of this agent. The chances of sexual and perinatal transmission have been estimated to be ~5% but shown in a prospective study to be only 1% between monogamous sexual partners, well below comparable rates for HIV and HBV infections. Moreover, sexual transmission appears to be confined to such subgroups as persons with multiple sexual partners and sexually transmitted diseases; for example, isolated clusters of sexually transmitted HCV infection have been reported in HIV-infected men who have sex with men. Breast-feeding does not increase the risk of HCV infection between an infected mother and her infant. Infection of health workers is not dramatically higher than among the general population; however, health workers are more likely to acquire HCV infection through accidental needle punctures, the efficiency of which is ~3%. Infection of household contacts is rare as well.

TABLE 332-4 High-Risk Populations for Whom HCV-Infection Screening is Recommended

Persons born between 1945 and 1965
Persons who have ever used injection drugs
Persons with HIV infection
Hemophiliacs treated with clotting factor concentrates prior to 1987
Persons who have ever undergone long-term hemodialysis
Persons with unexplained elevations of aminotransferase levels
Transfusion or transplantation recipients prior to July 1992
Recipients of blood or organs from a donor found to be positive for hepatitis C
Children born to women with hepatitis C
Health care, public safety, and emergency medical personnel following needle injury or mucosal exposure to HCV-contaminated blood
Sexual partners of persons with hepatitis C infection

Besides persons born between 1945 and 1965, other groups with an increased frequency of HCV infection are listed in **Table 332-4**. In immunosuppressed individuals, levels of anti-HCV may be undetectable, and a diagnosis may require testing for HCV RNA. Although new acute cases of hepatitis C are rare outside of the injection-drug using community, newly diagnosed cases are common among otherwise healthy persons who experimented briefly with injection drugs, as noted above, three or four decades earlier. Such instances usually remain unrecognized for years, until unearthed by laboratory screening for routine medical examinations, insurance applications, and attempted blood donation. Although, overall, the annual incidence of new HCV infections has continued to fall, the rate of new infections has been increasing since 2002, amplified by the recent epidemic of opioid use, in a new cohort of young injection drug users, age 15–24 years (accounting for more than two-thirds of all acute cases), who, unlike older cohorts, had not learned to take precautions to prevent bloodborne infections.

Hepatitis E This type of hepatitis, identified in India, Asia, Africa, the Middle East, and Central America, resembles hepatitis A in its primarily enteric mode of spread. The commonly recognized cases occur after contamination of water supplies such as after monsoon flooding, but sporadic, isolated cases occur. An epidemiologic feature that distinguishes HEV from other enteric agents is the rarity of secondary person-to-person spread from infected persons to their close contacts. Large waterborne outbreaks in endemic areas are linked to genotypes 1 and 2, arise in populations that are immune to HAV, favor young adults, and account for antibody prevalences of 30–80%. In nonendemic areas of the world, such as the United States, clinically apparent acute hepatitis E is extremely rare; however, during the 1988–1994 NHANES survey conducted by the U.S. Public Health Service, the prevalence of anti-HEV was 21%, reflecting subclinical infections, infection with genotypes 3 and 4, predominantly in older males (>60 years). In nonendemic areas, HEV accounts hardly at all for cases of sporadic (labeled "autochthonous" or indigenous) hepatitis; however, cases imported from endemic areas have been found in the United States. Evidence supports a zoonotic reservoir for HEV primarily in swine, which may account for the mostly subclinical infections in nonendemic areas. A previously unrecognized high distribution of HEV infection, linked to pork-product ingestion, has been discovered in western Europe (e.g., in Germany, an estimated annual incidence of 300,000 cases and a 17% prevalence of anti-HEV among adults; in France, a 22% prevalence of anti-HEV in healthy blood donors).

CLINICAL AND LABORATORY FEATURES

Symptoms and Signs Acute viral hepatitis occurs after an incubation period that varies according to the responsible agent. Generally, incubation periods for hepatitis A range from 15 to 45 days (mean, 4 weeks), for hepatitis B and D from 30 to 180 days (mean, 8–12 weeks), for hepatitis C from 15 to 160 days (mean, 7 weeks), and for hepatitis E from 14 to 60 days (mean, 5–6 weeks). The *prodromal symptoms* of acute viral hepatitis are systemic and quite variable. Constitutional symptoms of anorexia, nausea and vomiting, fatigue, malaise, arthralgias, myalgias, headache, photophobia, pharyngitis, cough, and coryza may precede the onset of jaundice by 1–2 weeks. The nausea, vomiting, and anorexia are frequently associated with alterations in olfaction and taste. A low-grade fever between 38° and 39°C (100°–102°F) is more often present in hepatitis A and E than in hepatitis B or C, except when hepatitis B is heralded by a serum sickness–like syndrome; rarely, a fever of 39.5°–40°C (103°–104°F) may accompany the constitutional symptoms. Dark urine and clay-colored stools may be noticed by the patient from 1–5 days before the onset of clinical jaundice.

With the onset of *clinical jaundice*, the constitutional prodromal symptoms usually diminish, but in some patients, mild weight loss (2.5–5 kg) is common and may continue during the entire icteric phase. The liver becomes enlarged and tender and may be associated with right upper quadrant pain and discomfort. Infrequently, patients present with a cholestatic picture, suggesting extrahepatic biliary obstruction. Splenomegaly and cervical adenopathy are present in 10–20% of patients with acute hepatitis. Rarely, a few spider angiomas appear during the icteric phase and disappear during convalescence. During the *recovery phase*, constitutional symptoms disappear, but usually some liver enlargement and abnormalities in liver biochemical tests are still evident. The duration of the posticteric phase is variable, ranging from 2 to 12 weeks, and is usually more prolonged in acute hepatitis B and C. Complete clinical and biochemical recovery is to be expected 1–2 months after all cases of hepatitis A and E and 3–4 months after the onset of jaundice in three-quarters of uncomplicated, self-limited cases of hepatitis B and C (among healthy adults, acute hepatitis B is self-limited in 95–99%, whereas hepatitis C is self-limited in only ~15–20%). In the remainder, biochemical recovery may be delayed. A substantial proportion of patients with viral hepatitis never become icteric.

Infection with HDV can occur in the presence of acute or chronic HBV infection; the duration of HBV infection determines the duration of HDV infection. When acute HDV and HBV infections occur simultaneously, clinical and biochemical features may be indistinguishable from those of HBV infection alone, although occasionally they are more severe. As opposed to patients with *acute* HBV infection, patients with *chronic* HBV infection can support HDV replication indefinitely, as when acute HDV infection occurs in the presence of a nonresolving acute HBV infection or, more commonly, when acute hepatitis D is superimposed on underlying chronic hepatitis B. In such cases, the HDV superinfection appears as a clinical exacerbation or an episode resembling acute viral hepatitis in someone already chronically infected with HBV. Superinfection with HDV in a patient with chronic hepatitis B often leads to clinical deterioration (see below).

In addition to superinfections with other hepatitis agents, acute hepatitis-like clinical events in persons with chronic hepatitis B may accompany spontaneous HBeAg to anti-HBe seroconversion or spontaneous reactivation (i.e., reversion from relatively nonreplicative to replicative infection). Such reactivations can occur as well in therapeutically immunosuppressed patients with chronic HBV infection when cytotoxic/immunosuppressive drugs are withdrawn; in these cases, restoration of immune competence is thought to allow resumption of previously checked cell-mediated immune cytolysis of HBV-infected hepatocytes. Occasionally, acute clinical exacerbations of chronic hepatitis B may represent the emergence of a precore mutant (see "Virology and Etiology"), and the subsequent course in such patients may be characterized by periodic exacerbations. Cytotoxic chemotherapy can lead to reactivation of chronic hepatitis C as well, and anti-TNF-α therapy can lead to reactivation of both hepatitis B and C.

Laboratory Features The serum aminotransferases aspartate aminotransferase (AST) and ALT (previously designated SGOT and SGPT) increase to a variable degree during the prodromal phase of acute viral hepatitis and precede the rise in bilirubin level (Figs. 332-2 and 332-4). The level of these enzymes, however, does not correlate well with the degree of liver cell damage. Peak levels vary from ~400 to ~4000 IU or more; these levels are usually reached at the time the patient is clinically icteric and diminish progressively during the recovery phase of acute hepatitis. The diagnosis of anicteric hepatitis is based on clinical features and on aminotransferase elevations.

Jaundice is usually visible in the sclera or skin when the serum bilirubin value is >43 μmol/L (2.5 mg/dL). When jaundice appears, the serum bilirubin typically rises to levels ranging from 85 to 340 μmol/L (5–20 mg/dL). The serum bilirubin may continue to rise despite falling serum aminotransferase levels. In most instances, the total bilirubin is equally divided between the conjugated and unconjugated fractions. Bilirubin levels >340 μmol/L (20 mg/dL) extending and persisting late into the course of viral hepatitis are more likely to be associated with severe disease. In certain patients with underlying hemolytic anemia, however, such as glucose-6-phosphate dehydrogenase deficiency and sickle cell anemia, a high serum bilirubin level is common, resulting from superimposed hemolysis. In such patients, bilirubin levels >513 μmol/L (30 mg/dL) have been observed and are not necessarily associated with a poor prognosis.

Neutropenia and lymphopenia are transient and are followed by a relative lymphocytosis. Atypical lymphocytes (varying between 2 and 20%) are common during the acute phase. Measurement of the prothrombin time (PT) is important in patients with acute viral hepatitis, because a prolonged value may reflect a severe hepatic synthetic defect, signify extensive hepatocellular necrosis, and indicate a worse prognosis. Occasionally, a prolonged PT may occur with only mild increases in the serum bilirubin and aminotransferase levels. Prolonged nausea and vomiting, inadequate carbohydrate intake, and poor hepatic glycogen reserves may contribute to hypoglycemia noted occasionally in patients with severe viral hepatitis. Serum alkaline phosphatase may be normal or only mildly elevated, whereas a fall in serum albumin is uncommon in uncomplicated acute viral hepatitis. In some patients, mild and transient steatorrhea has been noted, as well as slight microscopic hematuria and minimal proteinuria.

A diffuse but mild elevation of the γ globulin fraction is common during acute viral hepatitis. Serum IgG and IgM levels are elevated in about one-third of patients during the acute phase of viral hepatitis, but the serum IgM level is elevated more characteristically during acute hepatitis A. During the acute phase of viral hepatitis, antibodies to smooth muscle and other cell constituents may be present, and low titers of rheumatoid factor, nuclear antibody, and heterophile antibody can also be found occasionally. In hepatitis C and D, antibodies to LKM may occur; however, the species of LKM antibodies in the two types of hepatitis are different from each other as well as from the LKM antibody species characteristic of autoimmune hepatitis type 2 (Chap. 334). The autoantibodies in viral hepatitis are nonspecific and can also be associated with other viral and systemic diseases. In contrast, virus-specific antibodies, which appear during and after hepatitis virus infection, are serologic markers of diagnostic importance.

As described above, serologic tests are available routinely with which to establish a diagnosis of hepatitis A, B, D, and C. Tests for fecal or serum HAV are not routinely available. Therefore, a diagnosis of hepatitis A is based on detection of IgM anti-HAV during acute illness (Fig. 332-2). Rheumatoid factor can give rise to false-positive results in this test.

A diagnosis of HBV infection can usually be made by detection of HBsAg in serum. Infrequently, levels of HBsAg are too low to be detected during acute HBV infection, even with contemporary, highly sensitive immunoassays. In such cases, the diagnosis can be established by the presence of IgM anti-HBc.

The titer of HBsAg bears little relation to the severity of clinical disease. Indeed, an inverse correlation exists between the serum concentration of HBsAg and the degree of liver cell damage. For example, titers are highest in immunosuppressed patients, lower in patients with chronic liver disease (but higher in mild chronic than in severe chronic

hepatitis), and very low in patients with acute fulminant hepatitis. These observations suggest that in hepatitis B the degree of liver cell damage and the clinical course are related to variations in the patient's immune response to HBV rather than to the amount of circulating HBsAg. In immunocompetent persons, however, a correlation exists between markers of HBV *replication* and liver injury (see below).

Another important serologic marker in patients with hepatitis B is HBeAg. Its principal clinical usefulness is as an indicator of relative infectivity. Because HBeAg is invariably present during early acute hepatitis B, HBeAg testing is indicated primarily in chronic infection.

In patients with hepatitis B surface antigenemia of unknown duration (e.g., blood donors found to be HBsAg-positive) testing for IgM anti-HBc may be useful to distinguish between acute or recent infection (IgM anti-HBc-positive) and chronic HBV infection (IgM anti-HBc-negative, IgG anti-HBc-positive). A false-positive test for IgM anti-HBc may be encountered in patients with high-titer rheumatoid factor. Also, IgM anti-HBc may be reexpressed during acute reactivation of chronic hepatitis B.

Anti-HBs is rarely detectable in the presence of HBsAg in patients with *acute* hepatitis B, but 10–20% of persons with *chronic* HBV infection may harbor low-level anti-HBs. This antibody is directed not against the common group determinant, *a*, but against the heterotypic subtype determinant (e.g., HBsAg of subtype *ad* with anti-HBs of subtype *y*). In most cases, this serologic pattern cannot be attributed to infection with two different HBV subtypes but, instead, is thought (based on the clonal selection theory of antibody diversity) to reflect the stimulation of a related clone of antibody-forming cells and is not a harbinger of imminent HBsAg clearance. When such antibody is detected, its presence is of no recognized clinical significance (see "Virology and Etiology").

After immunization with hepatitis B vaccine, which consists of HBsAg alone, anti-HBs is the only serologic marker to appear. The commonly encountered serologic patterns of hepatitis B and their interpretations are summarized in **Table 332-5**. Tests for the detection of HBV DNA in liver and serum are now available. Like HBeAg, serum HBV DNA is an indicator of HBV replication, but tests for HBV DNA are more sensitive and quantitative. First-generation hybridization assays for HBV DNA had a sensitivity of 10^5–10^6 virions/mL, a relative threshold below which infectivity and liver injury are limited and HBeAg is usually undetectable. Currently, testing for HBV DNA has shifted from insensitive hybridization assays to amplification assays (e.g., the PCR-based assay, which can detect as few as 10 or 100 virions/mL); among the commercially available PCR assays, the most useful are those with the highest sensitivity (5–10 IU/mL) and the largest dynamic range (10^0–10^9 IU/mL). With increased sensitivity, amplification assays remain reactive well below the current 10^3–10^4 IU/mL threshold for infectivity and liver injury. These markers are useful in following the course of HBV replication in patients with chronic hepatitis B receiving antiviral chemotherapy **(Chap. 334)**. Except for the early decades of life after perinatally acquired HBV infection (see above), in immunocompetent adults with chronic hepatitis B, a general correlation exists between the level of HBV replication, as reflected by the level of serum HBV DNA, and the degree of liver injury. High-serum HBV DNA levels, increased expression of viral antigens, and necroinflammatory activity in the liver go hand in hand unless immunosuppression interferes with cytolytic T cell responses to virus-infected cells; reduction of HBV replication with antiviral drugs tends to be accompanied by an improvement in liver histology. Among patients with chronic hepatitis B, high levels of HBV DNA increase the risk of cirrhosis, hepatic decompensation, and hepatocellular carcinoma (see "Complications and Sequelae").

In patients with hepatitis C, an episodic pattern of aminotransferase elevation is common. A specific serologic diagnosis of hepatitis C can be made by demonstrating the presence in serum of anti-HCV. When contemporary immunoassays are used, anti-HCV can be detected in acute hepatitis C during the initial phase of elevated aminotransferase activity and remains detectable after recovery (rare) and during chronic infection (common). Nonspecificity can confound immunoassays for anti-HCV, especially in persons with a low prior probability of infection, such as volunteer blood donors, or in persons with circulating rheumatoid factor, which can bind nonspecifically to assay reagents; testing for HCV RNA can be used in such settings to distinguish between true-positive and false-positive anti-HCV determinations. Assays for HCV RNA are the most sensitive tests for HCV infection and represent the "gold standard" in establishing a diagnosis of hepatitis C. HCV RNA can be detected even before acute elevation of aminotransferase activity and before the appearance of anti-HCV in patients with acute hepatitis C. In addition, HCV RNA remains detectable indefinitely, continuously in most but intermittently in some, in patients with chronic hepatitis C (detectable as well in some persons with normal liver tests, i.e., inactive carriers). In the very small minority of patients with hepatitis C who lack anti-HCV, a diagnosis can be supported by detection of HCV RNA. If all these tests are negative and the patient has a well-characterized case of hepatitis after percutaneous exposure to blood or blood products, a diagnosis of hepatitis caused by an unidentified agent can be entertained.

Amplification techniques are required to detect HCV RNA. Currently, such target amplification (i.e., synthesis of multiple copies of the viral genome) is achieved by PCR, in which the viral RNA is reverse transcribed to complementary DNA and then amplified by repeated cycles of DNA synthesis. Quantitative PCR assays provide a measurement of relative "viral load"; current PCR assays have a sensitivity of 10 (lower limit of detection)-25 (lower limit of quantitation) IU/mL and a wide dynamic range (10–10^7 IU/mL). Determination of HCV RNA level is not a reliable marker of disease severity or prognosis but is helpful in predicting relative responsiveness to antiviral therapy. The same is true for determinations of HCV genotype **(Chap. 334)**. Of course, HCV RNA monitoring during and after antiviral therapy is the *sine qua non* for determining on-treatment and durable responsiveness.

A proportion of patients with hepatitis C have isolated anti-HBc in their blood, a reflection of a common risk in certain populations of exposure to multiple bloodborne hepatitis agents. The anti-HBc in such cases is almost

TABLE 332-5 Commonly Encountered Serologic Patterns of Hepatitis B Infection

HBsAg	ANTI-HBs	ANTI-HBc	HBeAg	ANTI-HBe	INTERPRETATION
+	–	IgM	+	–	Acute hepatitis B, high infectivity[a]
+	–	IgG	+	–	Chronic hepatitis B, high infectivity
+	–	IgG	–	+	1. Late acute or chronic hepatitis B, low infectivity 2. HBeAg-negative ("precore-mutant") hepatitis B (chronic or, rarely, acute)
+	+	+	+/–	+/–	1. HBsAg of one subtype and heterotypic anti-HBs (common) 2. Process of seroconversion from HBsAg to anti-HBs (rare)
–	–	IgM	+/–	+/–	1. Acute hepatitis B[a] 2. Anti-HBc "window"
–	–	IgG	–	+/–	1. Low-level hepatitis B carrier 2. Hepatitis B in remote past
–	+	IgG	–	+/–	Recovery from hepatitis B
–	+	–	–	–	1. Immunization with HBsAg (after vaccination) 2. Hepatitis B in the remote past (?) 3. False-positive

[a]IgM anti-HBc may reappear during acute reactivation of chronic hepatitis B.

Note: See text for abbreviations.

invariably of the IgG class and usually represents HBV infection in the remote past (HBV DNA undetectable); it rarely represents current HBV infection with low-level virus carriage. Detectable anti-HCV in the absence of HCV RNA signifies spontaneous or therapeutically induced recovery from ("cured") hepatitis C.

The presence of HDV infection can be identified by demonstrating intrahepatic HDV antigen or, more practically, an anti-HDV seroconversion (a rise in titer of anti-HDV or de novo appearance of anti-HDV). Circulating HDV antigen, also diagnostic of acute infection, is detectable only briefly, if at all. Because anti-HDV is often undetectable once HBsAg disappears, retrospective serodiagnosis of acute self-limited, simultaneous HBV and HDV infection is difficult. Early diagnosis of acute infection may be hampered by a delay of up to 30–40 days in the appearance of anti-HDV.

When a patient presents with acute hepatitis and has HBsAg and anti-HDV in serum, determination of the class of anti-HBc is helpful in establishing the relationship between infection with HBV and HDV. Although IgM anti-HBc does not distinguish *absolutely* between acute and chronic HBV infection, its presence is a reliable indicator of recent infection and its absence a reliable indicator of infection in the remote past. In simultaneous acute HBV and HDV infections, IgM anti-HBc will be detectable, whereas in acute HDV infection superimposed on chronic HBV infection, anti-HBc will be of the IgG class. Assays for HDV RNA, available in specialized laboratories and yet to be standardized, can be used to confirm HDV infection and to monitor treatment during chronic infection.

The serologic/virologic course of events during acute hepatitis E is entirely analogous to that of acute hepatitis A, with brief fecal shedding of virus and viremia and an early IgM anti-HEV response that predominates during approximately the first 3 months, but is eclipsed thereafter by long-lasting IgG anti-HEV. Diagnostic tests of varying reliability for hepatitis E are commercially available but used routinely primarily outside the United States; in the United States, diagnostic serologic/virologic assays can be performed at the Centers for Disease Control and Prevention or other specialized reference laboratories.

Liver biopsy is rarely necessary or indicated in acute viral hepatitis, except when the diagnosis is questionable or when clinical evidence suggests a diagnosis of chronic hepatitis.

A diagnostic algorithm can be applied in the evaluation of cases of acute viral hepatitis. A patient with acute hepatitis should undergo four serologic tests: HBsAg, IgM anti-HAV, IgM anti-HBc, and anti-HCV **(Table 332-6)**. The presence of HBsAg, with or without IgM anti-HBc, represents HBV infection. If IgM anti-HBc is present, the HBV infection is considered acute; if IgM anti-HBc is absent, the HBV infection is considered chronic. A diagnosis of acute hepatitis B can be made in the absence of HBsAg when IgM anti-HBc is detectable. A diagnosis of acute hepatitis A is based on the presence of IgM anti-HAV. If IgM anti-HAV coexists with HBsAg, a diagnosis of simultaneous HAV and HBV infections can be made; if IgM anti-HBc (with or without HBsAg) is detectable, the patient has simultaneous acute hepatitis A and B, and if IgM anti-HBc is undetectable, the patient has acute hepatitis A superimposed on chronic HBV infection. The presence of anti-HCV supports a diagnosis of acute hepatitis C. Occasionally, testing for HCV RNA or repeat anti-HCV testing later during the illness is necessary to establish the diagnosis. Absence of all serologic markers is consistent with a diagnosis of "non-A, non-B, non-C" hepatitis (no other proven human hepatitis viruses have been identified), if the epidemiologic setting is appropriate.

In patients with chronic hepatitis, initial testing should consist of HBsAg and anti-HCV. Anti-HCV supports and HCV RNA testing establishes the diagnosis of chronic hepatitis C. If a serologic diagnosis of chronic hepatitis B is made, testing for HBeAg and anti-HBe is indicated to evaluate relative infectivity. Testing for HBV DNA in such patients provides a more quantitative and sensitive measure of the level of virus replication, and therefore is very helpful during antiviral therapy **(Chap. 334)**. In patients with chronic hepatitis B and normal aminotransferase activity in the absence of HBeAg, serial testing over time is often required to distinguish between inactive carriage and HBeAg-negative chronic hepatitis B with fluctuating virologic and necroinflammatory activity. In persons with hepatitis B, testing for anti-HDV is useful in those with severe and fulminant disease, with severe chronic disease, with chronic hepatitis B and acute hepatitis-like exacerbations, with frequent percutaneous exposures, and from areas where HDV infection is endemic.

TABLE 332-6 Simplified Diagnostic Approach in Patients Presenting with Acute Hepatitis

SEROLOGIC TESTS OF PATIENT'S SERUM				
HBsAg	IgM ANTI-HAV	IgM ANTI-HBc	ANTI-HCV	DIAGNOSTIC INTERPRETATION
+	–	+	–	Acute hepatitis B
+	–	–	–	Chronic hepatitis B
+	+	–	–	Acute hepatitis A superimposed on chronic hepatitis B
+	+	+	–	Acute hepatitis A and B
–	+	–	–	Acute hepatitis A
–	+	+	–	Acute hepatitis A and B (HBsAg below detection threshold)
–	–	+	–	Acute hepatitis B (HBsAg below detection threshold)
–	–	–	+	Acute hepatitis C

Note: See text for abbreviations.

PROGNOSIS

Virtually all previously healthy patients with hepatitis A recover completely with no clinical sequelae. Similarly, in acute hepatitis B, 95–99% of previously healthy adults have a favorable course and recover completely. Certain clinical and laboratory features, however, suggest a more complicated and protracted course. Patients of advanced age and with serious underlying medical disorders may have a prolonged course and are more likely to experience severe hepatitis. Initial presenting features such as ascites, peripheral edema, and symptoms of hepatic encephalopathy suggest a poorer prognosis. In addition, a prolonged PT, low serum albumin level, hypoglycemia, and very high serum bilirubin values suggest severe hepatocellular disease. Patients with these clinical and laboratory features deserve prompt hospital admission. The case fatality rate in hepatitis A and B is very low (~0.1%) but is increased by advanced age and underlying debilitating disorders. Among patients ill enough to be hospitalized for acute hepatitis B, the fatality rate is 1%. Hepatitis C is less severe during the acute phase than hepatitis B and is more likely to be anicteric; fatalities are rare, but the precise case fatality rate is not known. In outbreaks of waterborne hepatitis E in India and Asia, the case fatality rate is 1–2% and up to 10–20% in pregnant women. Contributing to fulminant hepatitis E in endemic countries (but only very rarely or not at all in nonendemic countries) are instances of acute hepatitis E superimposed on underlying chronic liver disease ("acute-on-chronic" liver disease). Patients with simultaneous acute hepatitis B and D do not necessarily experience a higher mortality rate than do patients with acute hepatitis B alone; however, in several outbreaks of acute simultaneous HBV and HDV infection among injection drug users, the case fatality rate was ~5%. When HDV superinfection occurs in a person with chronic hepatitis B, the likelihood of fulminant hepatitis and death is increased substantially. Although the case fatality rate for hepatitis D is not known definitively, in outbreaks of severe HDV superinfection in isolated populations with a high hepatitis B carrier rate, a mortality rate >20% has been recorded.

COMPLICATIONS AND SEQUELAE

A small proportion of patients with hepatitis A experience *relapsing hepatitis* weeks to months after apparent recovery from acute hepatitis. Relapses are characterized by recurrence of symptoms, aminotransferase elevations, occasional jaundice, and

fecal excretion of HAV. Another unusual variant of acute hepatitis A is *cholestatic hepatitis*, characterized by protracted cholestatic jaundice and pruritus. Rarely, liver test abnormalities persist for many months, even up to 1 year. Even when these complications occur, hepatitis A remains self-limited and does not progress to chronic liver disease. During the prodromal phase of acute hepatitis B, a serum sickness–like syndrome characterized by arthralgia or arthritis, rash, angioedema, and, rarely, hematuria and proteinuria may develop in 5–10% of patients. This syndrome occurs before the onset of clinical jaundice, and these patients are often diagnosed erroneously as having rheumatologic diseases. The diagnosis can be established by measuring serum aminotransferase levels, which are almost invariably elevated, and serum HBsAg. As noted above, EMC is an immune-complex disease that can complicate chronic hepatitis C and is part of a spectrum of B cell lymphoproliferative disorders, which, in rare instances, can evolve to B cell lymphoma **(Chap. 104)**. Attention has been drawn as well to associations between hepatitis C and such cutaneous disorders as porphyria cutanea tarda and lichen planus. A mechanism for these associations is unknown. Finally, related to the reliance of HCV on lipoprotein secretion and assembly pathways and on interactions of HCV with glucose metabolism, HCV infection may be complicated by hepatic steatosis, hypercholesterolemia, insulin resistance (and other manifestations of the metabolic syndrome), and type 2 diabetes mellitus; both hepatic steatosis and insulin resistance appear to accelerate hepatic fibrosis and blunt responsiveness to interferon-based antiviral therapy **(Chap. 334)**.

The most feared complication of viral hepatitis is *fulminant hepatitis* (massive hepatic necrosis); fortunately, this is a rare event. Fulminant hepatitis is seen primarily in hepatitis B, D, and E, but rare fulminant cases of hepatitis A occur primarily in older adults and in persons with underlying chronic liver disease, including, according to some reports, chronic hepatitis B and C. Hepatitis B accounts for >50% of fulminant cases of viral hepatitis, a sizable proportion of which are associated with HDV infection and another proportion with underlying chronic hepatitis C. Fulminant hepatitis is hardly ever seen in hepatitis C, but hepatitis E, as noted above, can be complicated by fatal fulminant hepatitis in 1–2% of all cases and in up to 20% of cases in pregnant women. Patients usually present with signs and symptoms of encephalopathy that may evolve to deep coma. The liver is usually small and the PT excessively prolonged. The combination of rapidly shrinking liver size, rapidly rising bilirubin level, and marked prolongation of the PT, even as aminotransferase levels fall, together with clinical signs of confusion, disorientation, somnolence, ascites, and edema, indicates that the patient has hepatic failure with encephalopathy. Cerebral edema is common; brainstem compression, gastrointestinal bleeding, sepsis, respiratory failure, cardiovascular collapse, and renal failure are terminal events. The mortality rate is exceedingly high (>80% in patients with deep coma), but patients who survive may have a complete biochemical and histologic recovery. If a donor liver can be located in time, liver transplantation may be lifesaving in patients with fulminant hepatitis **(Chap. 338)**.

Documenting the disappearance of HBsAg after apparent clinical recovery from acute hepatitis B is particularly important. Before laboratory methods were available to distinguish between acute hepatitis and acute hepatitis-like exacerbations (*spontaneous reactivations*) of chronic hepatitis B, observations suggested that ~10% of previously healthy patients remained HBsAg-positive for >6 months after the onset of clinically apparent acute hepatitis B. One-half of these persons cleared the antigen from their circulations during the next several years, but the other 5% remained chronically HBsAg-positive. More recent observations suggest that the true rate of chronic infection after clinically apparent acute hepatitis B is as low as 1% in normal, immunocompetent, young adults. Earlier, higher estimates may have been confounded by inadvertent inclusion of acute exacerbations in chronically infected patients; these patients, chronically HBsAg-positive before exacerbation, were unlikely to seroconvert to HBsAg-negative thereafter. Whether the rate of chronicity is 10% or 1%, such patients have IgG anti-HBc in serum; anti-HBs is either undetected or detected at low titer against the opposite subtype specificity of the antigen (see "Laboratory Features"). These patients may (1) be inactive carriers; (2) have low-grade, mild chronic hepatitis; or (3) have moderate to severe chronic hepatitis with or without cirrhosis. The likelihood of remaining chronically infected after acute HBV infection is especially high among neonates, persons with Down's syndrome, chronically hemodialyzed patients, and immunosuppressed patients, including persons with HIV infection.

Chronic hepatitis is an important late complication of acute hepatitis B occurring in a small proportion of patients with acute disease but more common in those who present with chronic infection without having experienced an acute illness, as occurs typically after neonatal infection or after infection in an immunosuppressed host **(Chap. 334)**. The following clinical and laboratory features suggest progression of acute hepatitis to chronic hepatitis: (1) lack of complete resolution of clinical symptoms of anorexia, weight loss, fatigue, and the persistence of hepatomegaly; (2) the presence of bridging/interface or multilobular hepatic necrosis on liver biopsy during protracted, severe acute viral hepatitis; (3) failure of the serum aminotransferase, bilirubin, and globulin levels to return to normal within 6–12 months after the acute illness; and (4) the persistence of HBeAg for >3 months or HBsAg for >6 months after acute hepatitis.

Although acute hepatitis D infection does not increase the likelihood of chronicity of simultaneous acute hepatitis B, hepatitis D has the potential for contributing to the severity of chronic hepatitis B. Hepatitis D superinfection can transform inactive or mild chronic hepatitis B into severe, progressive chronic hepatitis and cirrhosis; it also can accelerate the course of chronic hepatitis B. Some HDV superinfections in patients with chronic hepatitis B lead to fulminant hepatitis. As defined in longitudinal studies over three decades, the annual rate of cirrhosis in patients with chronic hepatitis D is 4%. Although HDV and HBV infections are associated with severe liver disease, mild hepatitis and even inactive carriage have been identified in some patients, and the disease may become indolent beyond the early years of infection.

After acute HCV infection, the likelihood of remaining chronically *infected* approaches 85–90%. Although many patients with chronic hepatitis C have no symptoms, cirrhosis may develop in as many as 20% within 10–20 years of acute illness; in some series of cases reported by referral centers, cirrhosis has been reported in as many as 50% of patients with chronic hepatitis C. Among cirrhotic patients with chronic hepatitis C, the annual risk of hepatic decompensation is ~4%. Although chronic hepatitis C accounts for at least 40% of cases of chronic liver disease and of patients undergoing liver transplantation for end-stage liver disease in the United States and Europe, in the majority of patients with chronic hepatitis C, morbidity and mortality are limited during the initial 20 years after the onset of infection. Progression of chronic hepatitis C may be influenced by advanced age of acquisition, long duration of infection, immunosuppression, coexisting excessive alcohol use, concomitant hepatic steatosis, other hepatitis virus infection, or HIV co-infection. In fact, instances of severe and rapidly progressive chronic hepatitis B and C are being recognized with increasing frequency in patients with HIV infection **(Chap. 197)**. In contrast, neither HAV nor HEV causes chronic liver disease in immunocompetent hosts; however, cases of chronic hepatitis E (including cirrhosis and end-stage liver disease) have been observed in immunosuppressed organ-transplant recipients, persons receiving cytotoxic chemotherapy, and persons with HIV infection. Among patients with chronic hepatitis (e.g., caused by hepatitis B or C, alcohol, etc.) in endemic countries, hepatitis E has been reported as the cause of acute-on-chronic liver failure; however, in most experiences among patients from nonendemic countries, HEV has not been found to contribute to hepatic decompensation in patients with chronic hepatitis.

Persons with chronic hepatitis B, particularly those infected in infancy or early childhood and especially those with HBeAg and/or high-level HBV DNA, have an enhanced risk of hepatocellular carcinoma. The risks of cirrhosis and hepatocellular carcinoma increase with the level of HBV replication. The annual rate of hepatocellular carcinoma in patients with chronic hepatitis D and cirrhosis is ~3%. The risk of hepatocellular carcinoma is increased as well in patients with chronic hepatitis C, almost exclusively in patients with cirrhosis, and almost always after at least several decades, usually after three decades

of disease **(Chap. 78)**. Among such cirrhotic patients with chronic hepatitis C, the annual risk of hepatocellular carcinoma is ~1–4%.

Rare complications of viral hepatitis include pancreatitis, myocarditis, atypical pneumonia, aplastic anemia, transverse myelitis, and peripheral neuropathy. In children, hepatitis B may present rarely with anicteric hepatitis, a nonpruritic papular rash of the face, buttocks, and limbs, and lymphadenopathy (papular acrodermatitis of childhood or Gianotti-Crosti syndrome).

Rarely, autoimmune hepatitis **(Chap. 334)** can be triggered by a bout of otherwise self-limited acute hepatitis, as reported after acute hepatitis A, B, and C.

DIFFERENTIAL DIAGNOSIS

Viral diseases such as infectious mononucleosis; those due to cytomegalovirus, herpes simplex, and coxsackieviruses; and toxoplasmosis may share certain clinical features with viral hepatitis and cause elevations in serum aminotransferase and, less commonly, in serum bilirubin levels. Tests such as the differential heterophile and serologic tests for these agents may be helpful in the differential diagnosis if HBsAg, anti-HBc, IgM anti-HAV, and anti-HCV determinations are negative. Aminotransferase elevations can accompany almost any systemic viral infection; other rare causes of liver injury confused with viral hepatitis are infections with *Leptospira*, *Candida*, *Brucella*, *Mycobacteria*, and *Pneumocystis*. A complete drug history is particularly important because many drugs and certain anesthetic agents can produce a picture of either acute hepatitis or cholestasis **(Chap. 333)**. Equally important is a past history of unexplained "repeated episodes" of acute hepatitis. This history should alert the physician to the possibility that the underlying disorder is chronic hepatitis, for example autoimmune hepatitis **(Chap. 334)**. Alcoholic hepatitis must also be considered, but usually the serum aminotransferase levels are not as markedly elevated, and other stigmata of alcoholism may be present. The finding on liver biopsy of fatty infiltration, a neutrophilic inflammatory reaction, and "alcoholic hyaline" would be consistent with alcohol-induced rather than viral liver injury. Because acute hepatitis may present with right upper quadrant abdominal pain, nausea and vomiting, fever, and icterus, it is often confused with acute cholecystitis, common duct stone, or ascending cholangitis. Patients with acute viral hepatitis may tolerate surgery poorly; therefore, it is important to exclude this diagnosis, and in confusing cases, a percutaneous liver biopsy may be necessary before laparotomy. Viral hepatitis in the elderly is often misdiagnosed as obstructive jaundice resulting from a common duct stone or carcinoma of the pancreas. Because acute hepatitis in the elderly may be quite severe and the operative mortality high, a thorough evaluation including biochemical tests, radiographic studies of the biliary tree, and even liver biopsy may be necessary to exclude primary parenchymal liver disease. Another clinical constellation that may mimic acute hepatitis is right ventricular failure with passive hepatic congestion or hypoperfusion syndromes, such as those associated with shock, severe hypotension, and severe left ventricular failure. Also included in this general category is any disorder that interferes with venous return to the heart, such as right atrial myxoma, constrictive pericarditis, hepatic vein occlusion (Budd-Chiari syndrome), or venoocclusive disease. Clinical features are usually sufficient to distinguish among these vascular disorders and viral hepatitis. Acute fatty liver of pregnancy, cholestasis of pregnancy, eclampsia, and the HELLP (*h*emolysis, *e*levated *l*iver tests, and *l*ow *p*latelets) syndrome can be confused with viral hepatitis during pregnancy. Very rarely, malignancies metastatic to the liver can mimic acute or even fulminant viral hepatitis. Occasionally, genetic or metabolic liver disorders (e.g., Wilson's disease, α_1 antitrypsin deficiency) and nonalcoholic fatty liver disease are confused with acute viral hepatitis.

TREATMENT

Acute Viral Hepatitis

Most persons with acute hepatitis (especially hepatitis A, B, and E) recover spontaneously and do not require specific antiviral therapy. In hepatitis B, among previously healthy adults who present with clinically apparent acute hepatitis, recovery occurs in ~99%; therefore, antiviral therapy is not likely to improve the rate of recovery and is not required. In rare instances of severe acute hepatitis B, treatment with a nucleoside analogue at oral doses used to treat chronic hepatitis B **(Chap. 334)** has been attempted successfully. Although clinical trials have not been done to establish the efficacy or duration of this approach, most authorities would recommend institution of antiviral therapy with a nucleoside analogue (entecavir or tenofovir, the most potent and least resistance-prone agents) for severe, but not mild–moderate, acute hepatitis B. Treatment should continue until 3 months after HBsAg seroconversion or 6 months after HBeAg seroconversion.

In typical cases of acute hepatitis C, recovery is rare (~15–20% in most experiences), progression to chronic hepatitis is the rule, and small clinical trials during the era of interferon-based regimens suggested that antiviral therapy with courses (usually 24 weeks) of standard or pegylated interferon α monotherapy reduced the rate of chronicity considerably by inducing sustained responses in 30–70% of patients (according to a meta-analyses of published studies) and in up to 98% in a small German multicenter study (treatment initiated an average of 3 months after infection). In the current interferon-free therapy era, as of 2016, six different all-oral, brief-duration (most lasting 12 weeks), very well-tolerated, highly effective (sustained virologic response rates exceeding 90–95%) combination regimens (of polymerase inhibitors, protease inhibitors, and/or NS5A inhibitors) are available to treat patients with chronic hepatitis C **(see Chap. 334)**; the same regimens are available and recommended to treat patients with acute hepatitis C. Although the duration of therapy for acute hepatitis C has not been determined definitively, in a study of 20 patients, acute hepatitis C resolved after treatment lasting only 6 weeks. In 2016, the European Association for the Study of the Liver (EASL) recommended 8 weeks of treatment for acute hepatitis C with a genotype-appropriate **(see Chap. 334)** direct-acting antiviral regimen consisting of sofosbuvir plus one of the three approved NS5A inhibitors without ribavirin (12 weeks for patients with acute hepatitis C and either a baseline HCV RNA level >1 million IU/mL or HIV co-infection).

Because spontaneous recovery can occur and because most cases of acute hepatitis C are not clinically severe or rapidly progressive, delaying antiviral therapy of acute hepatitis C for at least 12–16 weeks and even up to 6 months (after which recovery is unlikely) is a recommended approach. Patients with jaundice, those with HCV genotype 1, women, earlier age of infection, lower level of HCV RNA, HBV co-infection, and absence of current injection-drug use are more likely to recover from acute hepatitis C, as are persons who have genetic markers associated with spontaneous recovery (*IL28B* CC haplotype). Because of the marked reduction over the past three decades in the frequency of acute hepatitis C, opportunities to identify and treat patients with acute hepatitis C are rare, except in two population subsets: (1) In health workers who sustain hepatitis C–contaminated needle sticks (occupational accidents), monitoring for ALT elevations and the presence of HCV RNA identify acute hepatitis C in ~3%, and this group should be treated; (2) in injection-drug users, the risk of acute hepatitis C has been on the rise, and the epidemic of opioid use has contributed to an amplification of HCV infection among drug users. Such patients are candidates for antiviral therapy, and efforts to combine antiviral therapy with drug-rehabilitation therapy have been very successful.

Notwithstanding these specific therapeutic considerations, in most cases of typical acute viral hepatitis, specific treatment generally is not necessary. Although hospitalization may be required for clinically severe illness, most patients do not require hospital care. Forced and prolonged bed rest is not essential for full recovery, but many patients will feel better with restricted physical activity. A high-calorie diet is desirable, and because many patients may experience nausea late in the day, the major caloric intake is best tolerated in the morning. Intravenous feeding is necessary in the acute stage if the patient has persistent vomiting and cannot maintain oral intake. Drugs capable of producing adverse reactions such as

cholestasis and drugs metabolized by the liver should be avoided. If severe pruritus is present, the use of the bile salt-sequestering resin cholestyramine is helpful. Glucocorticoid therapy has no value in acute viral hepatitis, even in severe cases, and may be deleterious, even increasing the risk of chronicity (e.g., of acute hepatitis B).

Physical isolation of patients with hepatitis to a single room and bathroom is rarely necessary except in the case of fecal incontinence for hepatitis A and E or uncontrolled, voluminous bleeding for hepatitis B (with or without concomitant hepatitis D) and C. Because most patients hospitalized with hepatitis A excrete little, if any, HAV, the likelihood of HAV transmission from these patients during their hospitalization is low. Therefore, burdensome *enteric precautions are no longer recommended*. Although gloves should be worn when the bed pans or fecal material of patients with hepatitis A are handled, these precautions do not represent a departure from sensible procedure and contemporary universal precautions for all hospitalized patients. For patients with hepatitis B and C, emphasis should be placed on blood precautions (i.e., avoiding direct, ungloved hand contact with blood and other body fluids). Enteric precautions are unnecessary. The importance of simple hygienic precautions such as hand washing cannot be overemphasized. Universal precautions that have been adopted for all patients apply to patients with viral hepatitis. Hospitalized patients may be discharged following substantial symptomatic improvement, a significant downward trend in the serum aminotransferase and bilirubin values, and a return to normal of the PT. Mild aminotransferase elevations should not be considered contraindications to the gradual resumption of normal activity.

In *fulminant hepatitis*, the goal of therapy is to support the patient by maintenance of fluid balance, support of circulation and respiration, control of bleeding, correction of hypoglycemia, and treatment of other complications of the comatose state in anticipation of liver regeneration and repair. Protein intake should be restricted, and oral lactulose administered. Glucocorticoid therapy has been shown in controlled trials to be ineffective. Likewise, exchange transfusion, plasmapheresis, human cross-circulation, porcine liver cross-perfusion, hemoperfusion, and extracorporeal liver-assist devices have not been proven to enhance survival. Meticulous intensive care that includes prophylactic antibiotic coverage is the one factor that appears to improve survival. Orthotopic liver transplantation is resorted to with increasing frequency, with excellent results, in patients with fulminant hepatitis **(Chap. 338)**. Fulminant hepatitis C is very rare; however, in fulminant hepatitis B, oral antiviral therapy has been used successfully, as reported anecdotally. In clinically severe hepatitis E (with jaundice and coagulopathy), successful therapy with ribavirin (600 mg twice daily, 15 mg/kg) has been reported anecdotally. Unfortunately, when fulminant hepatitis E occurs in pregnant women (as it does in up to 20% of pregnant women with acute hepatitis E), ribavirin, which is teratogenic, is contraindicated.

PROPHYLAXIS

Because application of therapy for acute viral hepatitis is limited and because antiviral therapy for chronic viral hepatitis is cumbersome, costly, and not effective in all patients **(Chap. 334)**, emphasis is placed on prevention through immunization. The prophylactic approach differs for each of the types of viral hepatitis. In the past, immunoprophylaxis relied exclusively on passive immunization with antibody-containing globulin preparations purified by cold ethanol fractionation from the plasma of hundreds of normal donors. Currently, for hepatitis A, B, and E, active immunization with vaccines is the preferable approach to prevention.

Hepatitis A Both passive immunization with IG and active immunization with killed vaccines are available. All preparations of IG contain anti-HAV concentrations sufficient to be protective. When administered before exposure or during the early incubation period, IG is effective in preventing clinically apparent hepatitis A. For postexposure prophylaxis of intimate contacts (household, sexual, institutional) of persons with hepatitis A, the administration of 0.02 mL/kg is recommended as early after exposure as possible; it may be effective even when administered as late as 2 weeks after exposure. Prophylaxis is not necessary for those who have already received hepatitis A vaccine, for casual contacts (office, factory, school, or hospital), for most elderly persons, who are very likely to be immune, or for those known to have anti-HAV in their serum. In day care centers, recognition of hepatitis A in children or staff should provide a stimulus for immunoprophylaxis in the center and in the children's family members. By the time most common-source outbreaks of hepatitis A are recognized, it is usually too late in the incubation period for IG to be effective; however, prophylaxis may limit the frequency of secondary cases. For travelers to tropical countries, developing countries, and other areas outside standard tourist routes, IG prophylaxis had been recommended before a vaccine became available. When such travel lasted <3 months, 0.02 mL/kg was given; for longer travel or residence in these areas, a dose of 0.06 mL/kg every 4–6 months was recommended. Administration of plasma-derived globulin is safe; all contemporary lots of IG are subjected to viral inactivation steps and must be free of HCV RNA as determined by PCR testing. Administration of IM lots of IG has not been associated with transmission of HBV, HCV, or HIV.

Formalin-inactivated vaccines made from strains of HAV attenuated in tissue culture have been shown to be safe, immunogenic, and effective in preventing hepatitis A. Hepatitis A vaccines are approved for use in persons who are at least 1 year old and appear to provide adequate protection beginning 4 weeks after a primary inoculation. If it can be given within 4 weeks of an expected exposure, such as by travel to an endemic area, hepatitis A vaccine is the preferred approach to *preexposure* immunoprophylaxis. If travel is more imminent, IG (0.02 mL/kg) should be administered at a different injection site, along with the first dose of vaccine. Because vaccination provides long-lasting protection (protective levels of anti-HAV should last 20 years after vaccination), persons whose risk will be sustained (e.g., frequent travelers or those remaining in endemic areas for prolonged periods) should be vaccinated, and vaccine should supplant the need for repeated IG injections. Shortly after its introduction, hepatitis A vaccine was recommended for children living in communities with a high incidence of HAV infection; in 1999, this recommendation was extended to include all children living in states, counties, and communities with high rates of HAV infection. As of 2006, the Advisory Committee on Immunization Practices of the U.S. Public Health Service recommended *routine hepatitis A vaccination of all children*. Other groups considered being at increased risk for HAV infection and who are candidates for hepatitis A vaccination include military personnel, populations with cyclic outbreaks of hepatitis A (e.g., Alaskan natives), employees of day care centers, primate handlers, laboratory workers exposed to hepatitis A or fecal specimens, and patients with chronic liver disease. Because of an increased risk of fulminant hepatitis A—observed in some experiences but not confirmed in others—among patients with chronic hepatitis C, patients with chronic hepatitis C are candidates for hepatitis A vaccination, as are persons with chronic hepatitis B. Other populations whose recognized risk of hepatitis A is increased should be vaccinated, including men who have sex with men, injection drug users, persons with clotting disorders who require frequent administration of clotting-factor concentrates, persons traveling from the United States to countries with high or intermediate hepatitis A endemicity, postexposure prophylaxis for contacts of persons with hepatitis A, and household members and other close contacts of adopted children arriving from countries with high and moderate hepatitis A endemicity. Recommendations for dose and frequency differ for the two approved vaccine preparations **(Table 332-7)**; all injections are IM. Hepatitis A vaccine has been reported to be effective in preventing secondary household and day care center–associated cases of acute hepatitis A. Because the vaccine provides long-lasting protection and is simpler to use, in 2006, the Immunization Practices Advisory Committee of the U.S. Public Health Service favored hepatitis A vaccine to IG for postexposure prophylaxis of healthy persons age 2–40 years; for younger or older persons, for immunosuppressed patients, and for patients with chronic liver disease, IG should continue to be used. In the United States, reported mortality resulting from hepatitis A

TABLE 332-7 Hepatitis A Vaccination Schedules

AGE, YEARS	NO. OF DOSES	DOSE	SCHEDULE, MONTHS
HAVRIX (GlaxoSmithKline)[a]			
1–18	2	720 ELU[b] (0.5 mL)	0, 6–12
≥19	2	1440 ELU (1 mL)	0, 6–12
VAQTA (Merck)			
1–18	2	25 units (0.5 mL)	0, 6–18
≥19	2	50 units (1 mL)	0, 6–18

[a]A combination of this hepatitis A vaccine and hepatitis B vaccine, TWINRIX, is licensed for simultaneous protection against both of these viruses among adults (age ≥18 years). Each 1-mL dose contains 720 ELU of hepatitis A vaccine and 20 μg of hepatitis B vaccine. These doses are recommended at months 0, 1, and 6. [b]Enzyme-linked immunoassay units.

declined in parallel with hepatitis A vaccine–associated reductions in the annual incidence of new infections.

Hepatitis B Until 1982, prevention of hepatitis B was based on *passive* immunoprophylaxis either with standard immunoglobulin, containing modest levels of anti-HBs, or hepatitis B immunoglobulin (HBIG), containing high-titer anti-HBs. The efficacy of standard IG has never been established and remains questionable; even the efficacy of HBIG, demonstrated in several clinical trials, has been challenged, and its contribution appears to be in reducing the frequency of clinical *illness*, not in preventing *infection*. The first vaccine for *active* immunization, introduced in 1982, was prepared from purified, noninfectious 22-nm spherical HBsAg particles derived from the plasma of healthy HBsAg carriers. In 1987, the plasma-derived vaccine was supplanted by a genetically engineered vaccine derived from recombinant yeast. The latter vaccine consists of HBsAg particles that are nonglycosylated but are otherwise indistinguishable from natural HBsAg; two recombinant vaccines are licensed for use in the United States. Current recommendations can be divided into those for preexposure and postexposure prophylaxis.

For *preexposure* prophylaxis against hepatitis B in settings of frequent exposure (health workers exposed to blood; first-responder public safety workers; hemodialysis patients and staff; residents and staff of custodial institutions for the developmentally handicapped; injection drug users; inmates of long-term correctional facilities; persons with multiple sexual partners or who have had a sexually transmitted disease; men who have sex with men; persons such as hemophiliacs who require long-term, high-volume therapy with blood derivatives; household and sexual contacts of persons with chronic HBV infection; persons living in or traveling extensively in endemic areas; unvaccinated children aged <18; unvaccinated children who are Alaskan natives, Pacific Islanders, or residents in households of first-generation immigrants from endemic countries; persons born in countries with a prevalence of HBV infection ≥2%; patients with chronic liver disease; persons <age 60 with diabetes mellitus [those ≥60 at the discretion of their physicians]; persons with end-stage renal disease; and persons with HIV infection), three IM (deltoid, not gluteal) injections of hepatitis B vaccine are recommended at 0, 1, and 6 months (other, optional schedules are summarized in Table 332-8). Pregnancy is *not* a contraindication to vaccination. In areas of low HBV endemicity such as the United States, despite the availability of safe and effective hepatitis B vaccines, a strategy of vaccinating persons in high-risk groups was not effective. The incidence of new hepatitis B cases continued to increase in the United States after the introduction of vaccines; <10% of all targeted persons in high-risk groups were actually vaccinated, and ~30% of persons with sporadic acute hepatitis B did not fall into any high-risk-group category. Therefore, to have an impact on the frequency of HBV infection in an area of low endemicity such as the United States, universal hepatitis B vaccination in childhood has been recommended. For unvaccinated children born after the implementation of universal infant vaccination, vaccination during early adolescence, at age 11–12 years, was recommended, and this recommendation has been extended to include all unvaccinated children age 0–19 years. In HBV-hyperendemic areas (e.g., Asia), universal vaccination of children has resulted in a marked (~70–90%) 30-year decline in complications of hepatitis B, including liver-related mortality and hepatocellular carcinoma.

The two available recombinant hepatitis B vaccines are comparable, one containing 10 μg of HBsAg (Recombivax-HB) and the other containing 20 μg of HBsAg (Engerix-B), and recommended doses for each injection vary for the two preparations (Table 332-8). Combinations of hepatitis B vaccine with other childhood vaccines are available as well (Table 332-8).

For unvaccinated persons sustaining an exposure to HBV, *postexposure* prophylaxis with a combination of HBIG (for rapid achievement of high-titer circulating anti-HBs) and hepatitis B vaccine (for achievement of long-lasting immunity as well as its apparent efficacy in attenuating clinical illness after exposure) is recommended. For *perinatal* exposure of infants born to HBsAg-positive mothers, a single dose of HBIG, 0.5 mL, should be administered IM in the thigh *immediately after birth*, followed by a complete course of three injections of recombinant hepatitis B vaccine (see doses above) to be started within the first 12 h of life. For those experiencing a direct percutaneous inoculation or transmucosal exposure to HBsAg-positive blood or body fluids (e.g., accidental *needle stick*, other mucosal penetration, or ingestion), a single IM dose of HBIG, 0.06 mL/kg, administered as soon after exposure as possible, is followed by a complete course of hepatitis B vaccine to begin within the first week. For pregnant mothers with high-level HBV DNA (>2×10^5 IU/mL), adding antiviral nucleoside analogues (e.g., pregnancy class B tenofovir, see Chap 334) during the third trimester of pregnancy reduces perinatal transmission even further. For persons exposed by *sexual* contact to a patient with acute hepatitis B, a single IM dose of HBIG, 0.06 mL/kg, should be given within 14 days of exposure,

TABLE 332-8 Preexposure Hepatitis B Vaccination Schedules

TARGET GROUP	NO. OF DOSES	DOSE	SCHEDULE, MONTHS
RECOMBIVAX-HB (Merck)[a]			
Infants, children (<1–10 years)	3	5 μg (0.5 mL)	0, 1–2, 4–6
Adolescents (11–19 years)	3 or 4	5 μg (0.5 mL)	0–2, 1–4, 4–6 *or* 0, 12, 24 *or* 0, 1, 2, 12
	Or		
Adults (≥20 years)	2	10 μg (1 mL)	0, 4–6 (age 11–15)
Hemodialysis patients[b]	3	10 μg (1 mL)	0–2, 1–4, 4–6
<20 years	3	5 μg (0.5 mL)	0, 1, 6
≥20 years	3	40 μg (4 mL)	0, 1, 6
ENGERIX-B (GlaxoSmithKline)[c]			
Infants, children (<1–10 years)	3 or 4	10 μg (0.5 mL)	0, 1–2, 4–6 *or* 0, 1, 2, 12
Adolescents (10–19 years)	3 or 4	10 μg (0.5 mL)	0, 1–2, 4–6 *or* 0, 12, 24 *or* 0, 1, 2, 12
Adults (≥20 years)	3 or 4	20 μg (1 mL)	0–2, 1–4, 4–6 or 0, 1, 2, 12
Hemodialysis patients[b]			
<20 years	4	10 μg (0.5 mL)	0, 1, 2, 6
≥20 years	4	40 μg (2 mL)	0, 1, 2, 6

[a]This manufacturer produces a licensed combination of hepatitis B vaccine and vaccines against *Haemophilus influenzae* type b and *Neisseria meningitides*, Comvax, for use in infants and young children. Please consult product insert for dose and schedule. [b]This group also includes other immunocompromised persons. [c]This manufacturer produces two licensed combination hepatitis B vaccines: (1) Twinrix, recombinant hepatitis B vaccine plus inactivated hepatitis A vaccine, is licensed for simultaneous protection against both of these viruses among adults (age ≥18 years). Each 1-mL dose contains 720 ELU of hepatitis A vaccine and 20 μg of hepatitis B vaccine. These doses are recommended at months 0, 1, and 6. (2) Pediarix, recombinant hepatitis B vaccine plus diphtheria and tetanus toxoid, pertussis, and inactivated poliovirus, is licensed for use in infants and young children. Please consult product insert for doses and schedules.

to be followed by a complete course of hepatitis B vaccine. When both HBIG and hepatitis B vaccine are recommended, they may be given at the same time but at separate sites. Testing adults for anti-HBs after a course of vaccine is advisable to document the acquisition of immunity, but, because hepatitis B vaccine immunogenicity is nearly universal in infants, postvaccination anti-HBs testing of children is not recommended.

The precise duration of protection afforded by hepatitis B vaccine is unknown; however, ~80–90% of immunocompetent adult vaccinees retain protective levels of anti-HBs for at least 5 years, and 60–80% for 10 years, and protective antibody has been documented to last for at least two decades after vaccination in infancy. Thereafter and even after anti-HBs becomes undetectable, protection persists against clinical hepatitis B, hepatitis B surface antigenemia, and chronic HBV infection. Currently, *booster* immunizations are not recommended routinely, except in immunosuppressed persons who have lost detectable anti-HBs or immunocompetent persons who sustain percutaneous HBsAg-positive inoculations after losing detectable antibody. Specifically, for hemodialysis patients, annual anti-HBs testing is recommended after vaccination; booster doses are recommended when anti-HBs levels fall to <10 mIU/mL. As noted above, for persons at risk of both hepatitis A and B, a combined vaccine is available containing 720 enzyme-linked immunoassay units (ELUs) of inactivated HAV and 20 μg of recombinant HBsAg (at 0, 1, and 6 months).

Hepatitis D Infection with hepatitis D can be prevented by vaccinating susceptible persons with hepatitis B vaccine. No product is available for immunoprophylaxis to prevent HDV superinfection in persons with chronic HBV infection; for them, avoidance of percutaneous exposures and limitation of intimate contact with persons who have HDV infection are recommended.

Hepatitis C IG is ineffective in preventing hepatitis C and is no longer recommended for postexposure prophylaxis in cases of perinatal, needle stick, or sexual exposure. Although prototype vaccines that induce antibodies to HCV envelope proteins have been developed, currently, hepatitis C vaccination is not feasible practically. Genotype and quasispecies viral heterogeneity, as well as rapid evasion of neutralizing antibodies by this rapidly mutating virus, conspire to render HCV a difficult target for immunoprophylaxis with a vaccine. Prevention of transfusion-associated hepatitis C has been accomplished by the following successively introduced measures: exclusion of commercial blood donors and reliance on a volunteer blood supply; screening donor blood with surrogate markers such as ALT (no longer recommended) and anti-HBc, markers that identify segments of the blood donor population with an increased risk of bloodborne infections; exclusion of blood donors in high-risk groups for AIDS and the introduction of anti-HIV screening tests; and progressively sensitive serologic and virologic screening tests for HCV infection.

In the absence of active or passive immunization, prevention of hepatitis C includes behavior changes and precautions to limit exposures to infected persons. Recommendations designed to identify patients with clinically inapparent hepatitis as candidates for medical management have as a secondary benefit the identification of persons whose contacts could be at risk of becoming infected. A so-called look-back program has been recommended to identify persons who were transfused before 1992 with blood from a donor found subsequently to have hepatitis C. In addition, anti-HCV testing is recommended for persons born between 1945 and 1965, anyone who received a blood transfusion or a transplanted organ before the introduction of second-generation screening tests in 1992, those who ever used injection drugs (or took other illicit drugs by noninjection routes), chronically hemodialyzed patients, persons with clotting disorders who received clotting factors made before 1987 from pooled blood products, persons with elevated aminotransferase levels, health workers exposed to HCV-positive blood or contaminated needles, recipients of blood or organs from a donor found to be positive for hepatitis C, persons with HIV infection, health care and public safety personnel following a needle stick or other nonpercutaneous exposure to HCV-infected material, sexual partners of persons with hepatitis C, and children born to HCV-positive mothers (Table 332-4).

For stable, monogamous sexual partners, sexual transmission of hepatitis C is unlikely, and sexual barrier precautions are not recommended. For persons with multiple sexual partners or with sexually transmitted diseases, the risk of sexual transmission of hepatitis C is increased, and barrier precautions (latex condoms) are recommended. A person with hepatitis C should avoid sharing such items as razors, toothbrushes, and nail clippers with sexual partners and family members. No special precautions are recommended for babies born to mothers with hepatitis C, and breast-feeding does not have to be restricted.

Hepatitis E Whether IG prevents hepatitis E remains undetermined. Safe and effective recombinant genotype 1 vaccines, which protect against other genotypes as well, have been developed and are available in endemic areas but not in the United States. Protection provided by the Chinese hepatitis E vaccine is long-lasting, documented in a clinical trial up to 4.5 years.

FURTHER READING

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