334 Chronic Hepatitis

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Chronic hepatitis represents a series of liver disorders of varying causes and severity in which hepatic inflammation and necrosis continue for at least 6 months. Milder forms are nonprogressive or only slowly progressive, while more severe forms may be associated with scarring and architectural reorganization, which, when advanced, lead ultimately to cirrhosis. Several categories of chronic hepatitis have been recognized. These include chronic viral hepatitis, drug-induced chronic hepatitis **(Chap. 333)**, and autoimmune chronic hepatitis. In many cases, clinical and laboratory features are insufficient to allow assignment into one of these three categories; these "idiopathic" cases are also believed to represent autoimmune chronic hepatitis. Finally, clinical and laboratory features of chronic hepatitis are observed occasionally in patients with such hereditary/metabolic disorders as Wilson's disease (copper overload), α_1 antitrypsin deficiency **(Chaps. 337 and 408)**, and nonalcoholic fatty liver disease **(Chap. 336)** and even occasionally in patients with alcoholic liver injury **(Chap. 335)**. Although all types of chronic hepatitis share certain clinical, laboratory, and histopathologic features, chronic viral and chronic autoimmune hepatitis are sufficiently distinct to merit separate discussions. **For discussion of acute hepatitis, see Chap. 332.**

CLASSIFICATION OF CHRONIC HEPATITIS

Common to all forms of chronic hepatitis are histopathologic distinctions based on localization and extent of liver injury. These vary from the milder forms, previously labeled *chronic persistent hepatitis* and *chronic lobular hepatitis*, to the more severe form, formerly called *chronic active hepatitis*. When first defined, these designations were believed to have prognostic implications, which were not corroborated by subsequent observations. Categorization of chronic hepatitis based primarily on histopathologic features has been replaced by a more informative classification based on a combination of clinical, serologic, and histologic variables. Classification of chronic hepatitis is based on (1) its *cause*; (2) its histologic activity, or *grade*; and (3) its degree of progression based on level of fibrosis, or *stage*. Thus, neither clinical features alone nor histologic features—requiring liver biopsy or noninvasive markers of fibrosis—alone are sufficient to characterize and distinguish among the several categories of chronic hepatitis.

CLASSIFICATION BY CAUSE

Clinical and serologic features allow the establishment of a diagnosis of *chronic viral hepatitis*, caused by hepatitis B, hepatitis B plus D, or hepatitis C; *autoimmune hepatitis*, including several subcategories, I and II, based on serologic distinctions; *drug-associated chronic hepatitis*; and a category of unknown cause, or *cryptogenic chronic hepatitis* **(Table 334-1)**. These are addressed in more detail below.

CLASSIFICATION BY GRADE

Grade, a histologic assessment of necroinflammatory activity, is based on examination of the liver biopsy. An assessment of important histologic features includes the degree of *periportal necrosis* and the disruption of the limiting plate of periportal hepatocytes by inflammatory cells (so-called *piecemeal necrosis* or *interface hepatitis*); the degree of confluent necrosis that links or forms bridges between vascular structures—between portal tract and portal tract or even more important bridges between portal tract and central vein—referred to as *bridging necrosis*; the degree of hepatocyte degeneration and focal necrosis within the lobule; and the degree of *portal inflammation*. Several scoring systems that take these histologic features into account have been devised, and the most popular are the histologic activity index (HAI), used commonly in the United States, and the METAVIR score, used in Europe **(Table 334-2)**. Based on the presence and degree of these features of histologic activity, chronic hepatitis can be graded as mild, moderate, or severe.

CLASSIFICATION BY STAGE

The stage of chronic hepatitis, which reflects the level of progression of the disease, is based on the degree of hepatic fibrosis. When fibrosis is so extensive that fibrous septa surround parenchymal nodules and alter the normal architecture of the liver lobule, the histologic lesion is defined as *cirrhosis*. Staging is based on the degree of fibrosis as categorized on a numerical scale 0–6 (HAI) or 0–4 (METAVIR) (Table 334-2). Several noninvasive approaches have been introduced to provide approximations of hepatic histologic stage, including serum biomarkers of fibrosis and imaging determinations of liver elasticity.

CHRONIC VIRAL HEPATITIS

Both the enterically transmitted forms of viral hepatitis, hepatitis A and E, are self-limited and do not cause chronic hepatitis (rare reports notwithstanding in which acute hepatitis A serves as a trigger for the onset of autoimmune hepatitis in genetically susceptible patients or in which hepatitis E **(Chap. 332)** can cause chronic liver disease in immunosuppressed hosts, for example, after liver transplantation). In contrast, the

TABLE 334-1 Clinical and Laboratory Features of Chronic Hepatitis

TYPE OF HEPATITIS	DIAGNOSTIC TEST(s)	AUTOANTIBODIES	THERAPY
Chronic hepatitis B	HBsAg, IgG anti-HBc, HBeAg, HBV DNA	Uncommon	IFN-α, PEG IFN-α Oral agents: First-line: entecavir, tenofovir Second-line: lamivudine, adefovir, telbivudine
Chronic hepatitis C	Anti-HCV, HCV RNA	Anti-LKM1[a]	PEG IFN-α plus ribavirin[b] Direct-acting oral agents: sofosbuvir, ledipasvir, velpatasvir ritonavir-boosted paritaprevir, ombitasvir, dasabavir elbasvir, grazoprevir daclatasvir, simeprevir
Chronic hepatitis D	Anti-HDV, HDV RNA, HBsAg, IgG anti-HBc	Anti-LKM3	IFN-α, PEG IFN-α[c]
Autoimmune hepatitis	ANA[d] (homogeneous), anti-LKM1 (±) Hyperglobulinemia	ANA, anti-LKM1 anti-SLA[e]	Prednisone, azathioprine
Drug-associated	—	Uncommon	Withdraw drug
Cryptogenic	All negative	None	Prednisone (?), azathioprine (?)

[a]Antibodies to liver-kidney microsomes type 1 (autoimmune hepatitis type II and some cases of hepatitis C). [b]Supplanted in almost all cases by combinations of the direct-acting antiviral agents listed (see *www.hcvguidelines.org*). [c]Early clinical trials suggested benefit of IFN-α therapy; PEG IFN-α is as effective, if not more so, and has supplanted standard IFN-α. [d]Antinuclear antibody (autoimmune hepatitis type I). [e]Antibodies to soluble liver antigen (autoimmune hepatitis type III).

Abbreviations: HBc, hepatitis B core; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus; HDV, hepatitis D virus; IFN-α, interferon α; IgG, immunoglobulin G; LKM, liver-kidney microsome; PEG IFN-α, pegylated interferon α; SLA, soluble liver antigen.

TABLE 334-2 Histologic Grading and Staging of Chronic Hepatitis

		HISTOLOGIC ACTIVITY INDEX (HAI)[a]		METAVIR[b]	
HISTOLOGIC FEATURE		**SEVERITY**	**SCORE**	**SEVERITY**	**SCORE**
Necroinflammatory Activity (grade)					
Periportal necrosis, including piecemeal necrosis and/or bridging necrosis (BN)		None	0	None	0
		Mild	1	Mild	1
		Mild/moderate	2	Moderate	2
		Moderate	3	Severe	3
		Severe	4		
				Bridging necrosis	Yes
					No
Intralobular necrosis	Confluent	—None	0	None or mild	0
		—Focal	1	Moderate	1
		—Zone 3 some	2	Severe	2
		—Zone 3 most	3		
		—Zone 3 + BN few	4		
		—Zone 3 + BN multiple	5		
		—Panacinar/multiacinar	6		
	Focal	—None	0		
		—≤1 focus/10× field	1		
		—2–4 foci/10× field	2		
		—5–10 foci/10× field	3		
		—>10 foci/10× field	4		
Portal Inflammation		None	0		
		Mild	1		
		Moderate	2		
		Moderate/marked	3		
		Marked	4		
		Total	0–18	A0–A3[c]	
Fibrosis (stage)					
None			0	F0	
Portal fibrosis—some			1	F1	
Portal fibrosis—most			2	F1	
Bridging fibrosis—few			3	F2	
Bridging fibrosis—many			4	F3	
Incomplete cirrhosis			5	F4	
Cirrhosis			6	F4	
		Total	6	4	

[a]Ishak K, Baptista A, Bianchi L, et al: Histologic grading and staging of chronic hepatitis. J Hepatol 22:696, 1995. [b]Bedossa P, Poynard T, French METAVIR Cooperative Study Group: An algorithm for grading activity in chronic hepatitis C. Hepatology 24:289, 1996. [c]Necroinflammatory grade: A0 = none; A1 = mild; A2 = moderate; A3 = severe.

entire clinicopathologic spectrum of chronic hepatitis occurs in patients with chronic viral hepatitis B and C as well as in patients with chronic hepatitis D superimposed on chronic hepatitis B.

CHRONIC HEPATITIS B

The likelihood of chronicity after acute hepatitis B varies as a function of age. Infection at birth is associated with clinically silent acute infection but a 90% chance of chronic infection, whereas infection in young adulthood in immunocompetent persons is typically associated with clinically apparent acute hepatitis but a risk of chronicity of only ~1%. Most cases of chronic hepatitis B among adults, however, occur in patients who never had a recognized episode of clinically apparent acute viral hepatitis. The degree of liver injury (grade) in patients with chronic hepatitis B is variable, ranging from none in inactive carriers to mild to moderate to severe. Among adults with chronic hepatitis B, histologic features are of prognostic importance. In one long-term study of patients with chronic hepatitis B, investigators found a 5-year survival rate of 97% for patients with mild chronic hepatitis, 86% for patients with moderate to severe chronic hepatitis, and only 55% for patients with chronic hepatitis and postnecrotic cirrhosis. The 15-year survival in these cohorts was 77%, 66%, and 40%, respectively. On the other hand, more recent observations do not allow us to be so sanguine about the prognosis in patients with mild chronic hepatitis; among such patients followed for 1–13 years, progression to more severe chronic hepatitis and cirrhosis has been observed in more than a quarter of cases.

More important to consider than histology alone in patients with chronic hepatitis B is the degree of hepatitis B virus (HBV) replication. As reviewed in **Chap. 332**, chronic HBV infection can occur in the presence or absence of serum hepatitis B e antigen (HBeAg), and generally, for both HBeAg-reactive and HBeAg-negative chronic hepatitis B, the level of HBV DNA correlates with the level of liver injury and risk of progression. In *HBeAg-reactive chronic hepatitis B*, two phases have been recognized based on the relative level of HBV replication. The relatively *replicative phase* is characterized by the presence in the serum of HBeAg and HBV DNA levels well in excess of 10^3–10^4 IU/mL, sometimes exceeding 10^9 IU/mL; by the presence in the liver of detectable intrahepatocyte nucleocapsid antigens (primarily hepatitis B core antigen [HBcAg]); by high infectivity; and by accompanying liver injury. In contrast, the relatively *nonreplicative phase* is characterized by the absence of the conventional serum marker of HBV replication (HBeAg), the appearance of anti-HBe, levels of HBV DNA below a threshold of ~10^3 IU/mL, the absence of intrahepatocytic HBcAg, limited infectivity, and minimal liver injury. Patients in the relatively replicative phase tend to have more severe chronic hepatitis, whereas those in the relatively nonreplicative phase tend to have minimal or mild chronic hepatitis or to be inactive hepatitis B carriers. The likelihood in a patient with HBeAg-reactive chronic hepatitis B of converting spontaneously from relatively replicative to nonreplicative infection is ~10% per year. Distinctions in HBV replication and in histologic category, however, do not always coincide. In patients with HBeAg-reactive chronic HBV infection, especially when acquired at birth or in early childhood, as recognized commonly in Asian countries, a dichotomy is common between very high levels of HBV replication during the early decades of life (when the level of apparent host immunologic tolerance of HBV is relatively high) and negligible levels of liver injury. Yet despite the relatively immediate, apparently benign nature of liver disease for many decades in this population, in the middle decades, activation of liver injury emerges as what appears to be the relative tolerance of the host to HBV declines, and these patients with childhood-acquired HBV infection are ultimately at increased risk later in life of cirrhosis, hepatocellular carcinoma (HCC) **(Chap. 78)**, and liver-related death. **A discussion of the pathogenesis of liver injury in patients with chronic hepatitis B appears in Chap. 332.**

HBeAg-negative chronic hepatitis B (i.e., chronic HBV infection with active virus replication, readily detectable HBV DNA but without HBeAg [anti-HBe-reactive]), is more common than HBeAg-reactive chronic hepatitis B in Mediterranean and European countries and in Asia (and, correspondingly, in HBV genotypes other than A). Compared to patients with HBeAg-reactive chronic hepatitis B, patients with HBeAg-negative chronic hepatitis B have HBV DNA levels several orders of magnitude lower (no more than 10^5–10^6 IU/mL) than those observed in the HBeAg-reactive subset. Most such cases represent precore or core-promoter mutations acquired

late in the natural history of the disease (mostly early-life onset; age range 40–55 years, older than that for HBeAg-reactive chronic hepatitis B); these mutations prevent translation of HBeAg from the precore component of the HBV genome (precore mutants) or are characterized by down-regulated transcription of precore mRNA (core-promoter mutants; **Chap. 332**). Although their levels of HBV DNA tend to be lower than among patients with HBeAg-reactive chronic hepatitis B, patients with HBeAg-negative chronic hepatitis B can have progressive liver injury (complicated by cirrhosis and HCC) and experience episodic reactivation of liver disease reflected in fluctuating levels of aminotransferase activity ("flares"). The biochemical and histologic activity of HBeAg-negative disease tends to correlate closely with levels of HBV replication, unlike the case mentioned above of Asian patients with HBeAg-reactive chronic hepatitis B during the early decades of their HBV infection. Worth reiterating, the level of HBV replication is the most important risk factor for the ultimate development of cirrhosis and HCC in both HBeAg-reactive (beyond the early decades of "relatively nonreplicative" infection) and HBeAg-negative patients. Although levels of HBV DNA are lower and more readily suppressed by therapy to undetectable levels in HBeAg-negative (compared to HBeAg-reactive) chronic hepatitis B, achieving sustained responses that permit discontinuation of antiviral therapy is less likely in HBeAg-negative patients (see below). Inactive carriers are patients with circulating hepatitis B surface antigen (HBsAg), normal serum aminotransferase levels, undetectable HBeAg, and levels of HBV DNA that are either undetectable or present at a threshold of $\leq 10^3$ IU/mL. This serologic profile occurs not only in inactive carriers but also in patients with HBeAg-negative chronic hepatitis B during periods of relative inactivity; distinguishing between the two requires sequential biochemical and virologic monitoring over many months.

The spectrum of *clinical features* of chronic hepatitis B is broad, ranging from asymptomatic infection to debilitating disease or even end-stage, fatal hepatic failure. As noted above, the onset of the disease tends to be insidious in most patients, with the exception of the very few in whom chronic disease follows failure of resolution of clinically apparent acute hepatitis B. **The clinical and laboratory features associated with progression from acute to chronic hepatitis B are discussed in Chap. 332.**

Fatigue is a common symptom, and persistent or intermittent *jaundice* is a common feature in severe or advanced cases. Intermittent deepening of jaundice and recurrence of malaise and anorexia, as well as worsening fatigue, are reminiscent of acute hepatitis; such exacerbations may occur spontaneously, often coinciding with evidence of virologic reactivation; may lead to progressive liver injury; and, when superimposed on well-established cirrhosis, may cause hepatic decompensation. Complications of cirrhosis occur in end-stage chronic hepatitis and include ascites, edema, bleeding gastroesophageal varices, hepatic encephalopathy, coagulopathy, and hypersplenism. Occasionally, these complications bring the patient to initial clinical attention. Extrahepatic complications of chronic hepatitis B, similar to those seen during the prodromal phase of acute hepatitis B, are associated with tissue deposition of circulating hepatitis B antigen–antibody immune complexes. These include arthralgias and arthritis, which are common, and the more rare purpuric cutaneous lesions (leukocytoclastic vasculitis), immune-complex glomerulonephritis, and generalized vasculitis (polyarteritis nodosa) **(Chaps. 332 and 356)**.

Laboratory features of chronic hepatitis B do not distinguish adequately between histologically mild and severe hepatitis. Aminotransferase elevations tend to be modest for chronic hepatitis B but may fluctuate in the range of 100–1000 units. As is true for acute viral hepatitis B, alanine aminotransferase (ALT) tends to be more elevated than aspartate aminotransferase (AST); however, once cirrhosis is established, AST tends to exceed ALT. Levels of alkaline phosphatase activity tend to be normal or only marginally elevated. In severe cases, moderate elevations in serum bilirubin (51.3–171 μmol/L [3–10 mg/dL]) occur. Hypoalbuminemia and prolongation of the prothrombin time occur in severe or end-stage cases. Hyperglobulinemia and detectable circulating autoantibodies are distinctly absent in chronic hepatitis B (in contrast to autoimmune hepatitis). **Viral markers of chronic HBV infection are discussed in Chap. 332.**

TREATMENT

Chronic Hepatitis B

Although progression to cirrhosis is more likely in severe than in mild or moderate chronic hepatitis B, all forms of chronic hepatitis B can be progressive, and progression occurs primarily in patients with active HBV replication. Moreover, in populations of patients with chronic hepatitis B who are at risk for HCC **(Chap. 78)**, the risk is highest for those with continued, high-level HBV replication and lower for persons in whom initially high-level HBV DNA falls spontaneously over time. Therefore, management of chronic hepatitis B is directed at suppressing the level of virus replication. Although clinical trials tend to focus on clinical endpoints achieved over 1–2 years (e.g., suppression of HBV DNA to undetectable levels, loss of HBeAg/HBsAg, improvement in histology, normalization of ALT), these short-term gains translate into reductions in the risk of clinical progression, hepatic decompensation, HCC, liver transplantation, and death; regression of cirrhosis and of esophageal varices have been documented to follow long-term pharmacologic suppression of HBV replication. In addition, restoration of impaired HBV-specific T-cell function has been shown following successful suppression of HBV replication with antiviral therapy. To date, seven drugs have been approved for treatment of chronic hepatitis B: injectable interferon (IFN) α and pegylated interferon (long-acting IFN bound to polyethylene glycol, PEG [PEG IFN]) and the oral agents lamivudine, adefovir dipivoxil, entecavir, telbivudine, and tenofovir disoproxil fumarate (TDF).

Antiviral therapy for hepatitis B has evolved rapidly since the mid-1990s, as has the sensitivity of tests for HBV DNA. When IFN and lamivudine were evaluated in clinical trials, HBV DNA was measured by insensitive hybridization assays with detection thresholds of 10^5–10^6 virions/mL; when adefovir, entecavir, telbivudine, tenofovir, and PEG IFN were studied in clinical trials, HBV DNA was measured by sensitive amplification assays (polymerase chain reaction [PCR]) with detection thresholds of 10^1–10^3 viral copies/mL or IU/mL. Recognition of these distinctions is helpful when comparing results of clinical trials that established the efficacy of these therapies (reviewed below in chronological order of publication of these efficacy trials).

INTERFERON

IFN-α was the first approved therapy (1992) for chronic hepatitis B. Although it is no longer used to treat hepatitis B, standard IFN is important historically, having provided important lessons about antiviral therapy in general. For immunocompetent adults with HBeAg-reactive chronic hepatitis B (who tend to have high-level HBV DNA [$>10^5$–10^6 virions/mL] and histologic evidence of chronic hepatitis on liver biopsy), a 16-week course of IFN given subcutaneously at a daily dose of 5 million units, or three times a week at a dose of 10 million units, resulted in a loss of HBeAg and hybridization-detectable HBV DNA (i.e., a reduction to levels below 10^5–10^6 virions/mL) in ~30% of patients, with a concomitant improvement in liver histology. Seroconversion from HBeAg to anti-HBe occurred in ~20%, and, in early trials, ~8% lost HBsAg. Successful IFN therapy and seroconversion were often accompanied by an acute hepatitis-like elevation in aminotransferase activity, postulated to result from enhanced cytolytic T cell clearance of HBV-infected hepatocytes. Relapse after successful therapy was rare (1 or 2%). The likelihood of responding to IFN was higher in patients with lower levels of HBV DNA and substantial elevations of ALT. Although children can respond as well as adults, IFN therapy was not effective in very young children infected at birth. Similarly, IFN therapy was not effective in immunosuppressed persons, Asian patients with neonatal acquisition of infection and minimal-to-mild ALT elevations, or patients with decompensated chronic hepatitis B (in whom such therapy was actually detrimental, sometimes precipitating decompensation, often associated with severe adverse effects). Among patients with HBeAg loss during therapy, long-term follow-up

demonstrated that 80% experienced eventual loss of HBsAg (i.e., all serologic markers of infection, and normalization of ALT over a 9-year posttreatment period). In addition, improved long-term and complication-free survival as well as a reduction in the frequency of HCC were documented among IFN responders, supporting the conclusion that successful antiviral therapy improves the natural history of chronic hepatitis B.

Initial trials of brief-duration IFN therapy in patients with *HBeAg-negative chronic hepatitis B* were disappointing, suppressing HBV replication transiently during therapy but almost never resulting in sustained antiviral responses. In subsequent IFN trials among patients with HBeAg-negative chronic hepatitis B, however, more protracted courses, lasting up to 1.5 years, were reported to result in sustained remissions documented to last for several years, with suppressed HBV DNA and aminotransferase activity, in ~20%.

Complications of IFN therapy include systemic "flu-like" symptoms; marrow suppression; emotional lability (irritability, depression, anxiety); autoimmune reactions (especially autoimmune thyroiditis); and miscellaneous side effects such as alopecia, rashes, diarrhea, and numbness and tingling of the extremities. With the possible exception of autoimmune thyroiditis, all these side effects are reversible upon dose lowering or cessation of therapy.

Although no longer competitive with the newer generation of antivirals, IFN did represent the first successful antiviral approach and set a standard against which to measure subsequent drugs in the achievement of durable virologic, serologic, biochemical, and histologic responses; consolidation of virologic and biochemical benefit in the ensuing years after therapy; and improvement in the natural history of chronic hepatitis B. Standard IFN has been supplanted by long-acting PEG IFN (see below), and IFN nonresponders are now treated with one of the newer oral nucleoside analogues.

LAMIVUDINE

The first of the nucleoside analogues to be approved (in 1998) for hepatitis B, the dideoxynucleoside lamivudine inhibits reverse transcriptase activity of both HIV and HBV and is an effective agent for patients with chronic hepatitis B. Although generally superseded by newer, more potent, less resistance-prone agents, lamivudine is still used in regions of the world where newer agents are not yet available or affordable. In clinical trials among patients with HBeAg-reactive chronic hepatitis B, lamivudine therapy at daily doses of 100 mg for 48–52 weeks suppressed HBV DNA by a median of ~5.5 $\log_{10}$ copies/mL and to undetectable levels, as measured by PCR amplification assays, in ~40% of patients. Therapy was associated with HBeAg loss in 32–33%, HBeAg seroconversion (i.e., conversion from HBeAg-reactive to anti-HBe-reactive) in 16–21%, normalization of ALT in 40–75%, improvement in histology in 50–60%, retardation in hepatic fibrosis in 20–30%, and prevention of progression to cirrhosis. HBeAg responses occur even in patients resistant to IFN (e.g., those with high-level HBV DNA) or who failed in the past to respond to it. As is true for IFN therapy of chronic hepatitis B, patients with near-normal ALT activity tend not to experience HBeAg responses (despite suppression of HBV DNA), whereas those with ALT levels exceeding 5 × the upper limit of normal can expect 1-year HBeAg seroconversion rates of 50–60%. Generally, HBeAg seroconversions are confined to patients who achieve suppression of HBV DNA to $<10^4$ copies/mL (equivalent to ~10^3 IU/mL). Lamivudine-associated HBeAg responses are accompanied by a delayed posttreatment HBsAg seroconversion rate comparable to that seen after IFN-induced HBeAg responses. Among Western patients who undergo HBeAg responses during a year-long course of therapy and in whom the response is sustained for 4–6 months after cessation of therapy, the response is durable thereafter in the vast majority (>80%); therefore, the achievement of an HBeAg response represents a viable stopping point in therapy. Reduced durability has been reported in Asian patients; therefore, to support the durability of HBeAg responses, patients should receive a period of consolidation therapy of ≥6 months in Western patients and ≥1 year in Asian patients after HBeAg seroconversion (see treatment guidelines below). Close posttreatment monitoring is necessary to identify HBV reactivation promptly and to resume therapy. If HBeAg is unaffected by lamivudine therapy, the current approach is to continue therapy until an HBeAg response occurs, but long-term therapy may be required to suppress HBV replication and, in turn, limit liver injury; HBeAg seroconversions can increase to a level of 50% after 5 years of therapy. Histologic improvement continues to accrue with therapy beyond the first year; after a cumulative course of 3 years of lamivudine therapy, necroinflammatory activity is reduced in the majority of patients, and even cirrhosis has been shown to regress to precirrhotic stages in as many as three-quarters of patients.

Losses of HBsAg have been few during the first year of lamivudine therapy, and this observation had been cited as an advantage of IFN-based over lamivudine therapy; however, in head-to-head comparisons between standard IFN and lamivudine monotherapy, HBsAg losses were rare in both groups. Trials in which lamivudine and IFN were administered in combination failed to show a benefit of combination therapy over lamivudine monotherapy for either treatment-naïve patients or prior IFN nonresponders.

In patients with *HBeAg-negative chronic hepatitis B* (i.e., in those with precore and core-promoter HBV mutations), 1 year of lamivudine therapy results in HBV DNA suppression and normalization of ALT in three-quarters of patients and in histologic improvement in approximately two-thirds. Therapy has been shown to suppress HBV DNA by ~4.5 $\log_{10}$ copies/mL (baseline HBV DNA levels are lower than in patients with HBeAg-reactive hepatitis B) and to undetectable levels in ~70%, as measured by sensitive PCR amplification assays. Lacking HBeAg at the outset, patients with HBeAg-negative chronic hepatitis B cannot achieve an HBeAg response—a stopping point in HBeAg-reactive patients; almost invariably, when therapy is discontinued, reactivation is the rule. Therefore, these patients require long-term therapy; with successive years, the proportion with suppressed HBV DNA and normal ALT increases.

Clinical and laboratory side effects of lamivudine are negligible and indistinguishable from those observed in placebo recipients. Still, lamivudine doses should be reduced in patients with reduced creatinine clearance. During lamivudine therapy, transient ALT elevations, resembling those seen during IFN therapy and during spontaneous HBeAg-to-anti-HBe seroconversions, occur in one-fourth of patients. These ALT elevations may result from restored cytolytic T cell activation permitted by suppression of HBV replication. Similar ALT elevations, however, occurred at an identical frequency in placebo recipients; however, ALT elevations associated with HBeAg seroconversion in clinical trials were confined to lamivudine-treated patients. When therapy is stopped after a year of therapy, two- to threefold ALT elevations occur in 20–30% of lamivudine-treated patients, representing renewed liver-cell injury as HBV replication returns. Although these posttreatment flares are almost always transient and mild, rare severe exacerbations, especially in cirrhotic patients, have been observed, mandating close and careful clinical and virologic monitoring after discontinuation of treatment. Many authorities caution against discontinuing therapy in patients with cirrhosis, in whom posttreatment flares could precipitate decompensation.

Long-term monotherapy with lamivudine is associated with methionine-to-valine (M204V) or methionine-to-isoleucine (M204I) mutations, primarily at amino acid 204 in the tyrosine-methionine-aspartate-aspartate (YMDD) motif of the C domain of HBV DNA polymerase, analogous to mutations that occur in HIV-infected patients treated with this drug. During a year of therapy, YMDD mutations occur in 15–30% of patients; the frequency increases with each year of therapy, reaching 70% at year 5. Ultimately, patients with YMDD mutants experience degradation of clinical, biochemical, and histologic responses; therefore, if treatment is begun with lamivudine monotherapy, the emergence of lamivudine resistance, reflected clinically by a breakthrough from suppressed levels of HBV DNA and ALT, is managed by adding another antiviral to which YMDD variants are sensitive (e.g., adefovir, tenofovir; see below).

Currently, although lamivudine is very safe and still used widely in other parts of the world, in the United States and Europe, lamivudine has been eclipsed by more potent antivirals that have superior resistance profiles (see below); it is no longer recommended as first-line therapy. Still, as the first successful oral antiviral agent for use in hepatitis B, lamivudine provided proof of principle that polymerase inhibitors can achieve virologic, serologic, biochemical, and histologic benefits. In addition, lamivudine has been shown to be effective in the treatment of patients with decompensated hepatitis B (for whom IFN is contraindicated), in some of whom decompensation can be reversed. Moreover, among patients with cirrhosis or advanced fibrosis, lamivudine has been shown to be effective in reducing the risk of progression to hepatic decompensation and, marginally, the risk of HCC. In the half decade following the introduction in the United States of lamivudine therapy for hepatitis B, referral of patients with HBV-associated end-stage liver disease for liver transplantation was reduced by ~30%, supporting further the beneficial impact of oral antiviral therapy on the natural history of chronic hepatitis B.

Because lamivudine monotherapy can result universally in the rapid emergence of YMDD variants in persons with HIV infection, patients with chronic hepatitis B should be tested for anti-HIV prior to therapy; if HIV infection is identified, lamivudine monotherapy at the HBV daily dose of 100 mg is contraindicated. These patients should be treated for both HIV and HBV with an HIV drug regimen that includes or is supplemented by at least two drugs active against HBV; antiretroviral therapy (ART) often contains two drugs with antiviral activity against HBV (e.g., tenofovir and emtricitabine), but if lamivudine is part of the regimen, the daily dose should be 300 mg **(Chap. 197)**. The safety of lamivudine during pregnancy has not been established; however, the drug is not teratogenic in rodents and has been used safely in pregnant women with HIV infection and with HBV infection. Administration of lamivudine during the last months of pregnancy to mothers with high-level hepatitis B viremia ($\geq 10^8$ IU/mL) can reduce the likelihood of perinatal transmission of hepatitis B.

ADEFOVIR DIPIVOXIL

At an oral daily dose of 10 mg, the acyclic nucleotide analogue adefovir dipivoxil, the prodrug of adefovir (approved for hepatitis B in 2002), reduces HBV DNA by ~3.5–4 $\log_{10}$ copies/mL and is equally effective in treatment-naïve patients and prior IFN nonresponders. In HBeAg-reactive chronic hepatitis B, a 48-week course of adefovir dipivoxil was shown to achieve histologic improvement (and reduce the progression of fibrosis) and normalization of ALT in just over one-half of patients, HBeAg seroconversion in 12%, HBeAg loss in 23%, and suppression to an undetectable level of HBV DNA in 13–21%, as measured by PCR. Similar to IFN and lamivudine, adefovir dipivoxil is more likely to achieve an HBeAg response in patients with high baseline ALT; among adefovir-treated patients with ALT level >5 × the upper limit of normal, HBeAg seroconversions occurred in 25%. The durability of adefovir-induced HBeAg responses is high (91% in one study); therefore, HBeAg response can be relied upon as a stopping point for adefovir therapy, after a period of consolidation therapy, as outlined above. Although data on the impact of additional therapy beyond 1 year are limited, biochemical, serologic, and virologic outcomes improve progressively as therapy is continued.

In patients with *HBeAg-negative chronic hepatitis B*, a 48-week course of 10 mg/d of adefovir dipivoxil resulted in histologic improvement in two-thirds, normalization of ALT in three-fourths, and suppression of HBV DNA to PCR-undetectable levels in one-half to two-thirds. As was true for lamivudine, because HBeAg responses—a potential stopping point—cannot be achieved in this group, reactivation is the rule when adefovir therapy is discontinued, and indefinite, long-term therapy is required. Treatment beyond the first year consolidates the gain of the first year; after 5 years of therapy, improvement in hepatic inflammation and regression of fibrosis were observed in three-fourths of patients, ALT was normal in 70%, and HBV DNA was undetectable in almost 70%. In one study, stopping adefovir after 5 years was followed by sustained suppression of HBV DNA and ALT, but most HBeAg-negative patients are treated indefinitely unless HBsAg loss, albeit very rare, is achieved.

Adefovir contains a flexible acyclic linker instead of the L-nucleoside ring of lamivudine, avoiding steric hindrance by mutated amino acids. In addition, the molecular structure of phosphorylated adefovir is very similar to that of its natural substrate; therefore, mutations to adefovir would also affect binding of the natural substrate, dATP. Hypothetically, these are among the reasons that resistance to adefovir dipivoxil is much less likely than resistance to lamivudine; no resistance was encountered in 1 year of clinical trial therapy. In subsequent years, however, adefovir resistance begins to emerge (asparagine to threonine at amino acid 236 [N236T] and alanine to valine or threonine at amino acid 181 [A181V/T], primarily), occurring in 2.5% after 2 years, but in 29% after 5 years of therapy (reported in HBeAg-negative patients). Among patients co-infected with HBV and HIV and who have normal CD4+ T cell counts, adefovir dipivoxil is effective in suppressing HBV dramatically (by 5 $\log_{10}$ in one study). Moreover, adefovir dipivoxil is effective in lamivudine-resistant, YMDD-mutant HBV and can be used when such lamivudine-induced variants emerge. When lamivudine resistance occurs, adding adefovir (i.e., maintaining lamivudine to preempt the emergence of adefovir resistance) is superior to switching to adefovir. Almost invariably, patients with adefovir-induced HBV mutations respond to lamivudine (or newer agents, such as entecavir, see below). When, in the past, adefovir had been evaluated as therapy for HIV infection, doses of 60–120 mg were required to suppress HIV, and, at these doses, the drug was nephrotoxic. Even at 30 mg/d, creatinine elevations of 44 µmol/L (0.5 mg/dL) occurred in 10% of patients; however, at the HBV-effective dose of 10 mg, such creatinine elevations are rarely encountered. If any nephrotoxicity does occur, it rarely appears before 6–8 months of therapy. Although renal tubular injury is a rare potential side effect, and although creatinine monitoring is recommended during treatment, the therapeutic index of adefovir dipivoxil is high, and the nephrotoxicity observed in clinical trials at higher doses was reversible. For patients with underlying renal disease, frequency of administration of adefovir dipivoxil should be reduced to every 48 h for creatinine clearances of 30–49 mL/min; to every 72 h for creatinine clearances of 10–29 mL/min; and to once a week, following dialysis, for patients undergoing hemodialysis. Adefovir dipivoxil is very well tolerated, and ALT elevations during and after withdrawal of therapy are similar to those observed and described above in clinical trials of lamivudine. An advantage of adefovir is its relatively favorable resistance profile; however, it is not as potent as the other approved oral agents, it does not suppress HBV DNA as rapidly or as uniformly as the others, it is the least likely of all agents to result in HBeAg seroconversion, and 20–50% of patients fail to suppress HBV DNA by 2 $\log_{10}$ ("primary nonresponders"). For these reasons, adefovir, which has been supplanted in both treatment-naïve and lamivudine-resistant patients by the more potent, less resistance-prone nucleotide analogue tenofovir (see below), is no longer recommended as first-line therapy.

PEGYLATED IFN

After long-acting PEG IFN was shown to be effective in the treatment of hepatitis C (see below), this more convenient drug was evaluated in the treatment of chronic hepatitis B. Once-a-week PEG IFN is more effective than the more frequently administered, standard IFN, and several large-scale trials of PEG IFN versus oral nucleoside analogues were conducted among patients with HBeAg-reactive and HBeAg-negative chronic hepatitis B.

In HBeAg-reactive chronic hepatitis B, two large-scale studies were done. In one study, PEG IFN-α 2b (100 µg weekly for 32 weeks, then 50 µg weekly for another 20 weeks for a total of 52 weeks) was evaluated against a comparison arm of combination PEG IFN with oral lamivudine in 307 subjects. The other study involved PEG IFN-α 2a (180 µg weekly for 48 weeks) in 814 primarily Asian patients, three-fourths of whom had ALT ≥2 × the upper limit of normal, with

comparison arms of lamivudine monotherapy and combination PEG IFN plus lamivudine. At the end of therapy (48–52 weeks) in the PEG IFN monotherapy arms, HBeAg loss occurred in ~30%, HBeAg seroconversion in 22–27%, undetectable HBV DNA (<400 copies/mL by PCR) in 10–25%, normal ALT in 34–39%, and a mean reduction in HBV DNA of 2 $\log_{10}$ copies/mL (PEG IFN-α 2b) to 4.5 $\log_{10}$ copies/mL (PEG IFN-α 2a). Six months after completing PEG IFN monotherapy in these trials, HBeAg losses were present in ~35%, HBeAg seroconversion in ~30%, undetectable HBV DNA in 7–14%, normal ALT in 32–41%, and a mean reduction in HBV DNA of 2–2.4 $\log_{10}$ copies/mL. Although the combination of PEG IFN and lamivudine was superior at the end of therapy in one or more serologic, virologic, or biochemical outcomes, neither the combination arm (in both studies) nor the lamivudine monotherapy arm (in the PEG IFN-α 2a trial) demonstrated any benefit compared to the PEG IFN monotherapy arms 6 months after therapy. Moreover, HBsAg seroconversion occurred in 3–7% of PEG IFN recipients (with or without lamivudine); some of these seroconversions were identified by the end of therapy, but many were identified during the post-treatment follow-up period. The likelihood of HBeAg loss in PEG IFN-treated HBeAg-reactive patients is associated with HBV genotype A > B > C > D (shown for PEG IFN-α2b but not for α-2a). PEG IFN-α 2a was approved in the US for hepatitis B in 2005; PEG IFN-α 2b, not approved for hepatitis B in the US, is used in other countries.

Based on these results, some authorities concluded that PEG IFN monotherapy should be the first-line therapy of choice in HBeAg-reactive chronic hepatitis B; however, this conclusion has been challenged. Although a finite, 1-year course of PEG IFN results in a higher rate of sustained response (6 months after treatment) than is achieved with oral nucleoside/nucleotide analogue therapy, the comparison is confounded by the fact that oral agents are not discontinued at the end of 1 year. Instead, taken orally and free of side effects, therapy with oral agents is extended indefinitely or until after the occurrence of an HBeAg response. The rate of HBeAg responses after 2 years of oral-agent nucleoside analogue therapy is at least as high as, if not higher than, that achieved with PEG IFN after 1 year; favoring oral agents is the absence of injections, difficult-to-tolerate side effects, and laboratory monitoring as well as lower direct and indirect medical care costs and inconvenience. The association of HBsAg responses with PEG IFN therapy occurs in such a small proportion of patients that subjecting everyone to PEG IFN for the marginal gain of HBsAg responses during or immediately after therapy in such a very small minority is questionable. Moreover, HBsAg responses occur in a comparable proportion of patients treated with early-generation nucleoside/nucleotide analogues in the years *after* therapy, and, with the newer, more potent nucleoside analogues, the frequency of HBsAg loss during the first year of therapy equals that of PEG IFN and is exceeded during year 2 and beyond (see below). Of course, resistance is not an issue during PEG IFN therapy, but the risk of resistance is much lower with new agents (≤1% up to 3–8 years in previously treatment-naïve, entecavir-treated and 0% of tenofovir-treated patients; see below). Finally, the level of HBV DNA inhibition that can be achieved with the newer agents, and even with lamivudine, exceeds that which can be achieved with PEG IFN, in some cases by several orders of magnitude.

In HBeAg-negative chronic hepatitis B, a trial of PEG IFN-α 2a (180 μg weekly for 48 weeks versus comparison arms of lamivudine monotherapy and of combination therapy) in 564 patients showed that PEG IFN monotherapy resulted at the end of therapy in suppression of HBV DNA by a mean of 4.1 $\log_{10}$ copies/mL, undetectable HBV DNA (<400 copies/mL by PCR) in 63%, normal ALT in 38%, and loss of HBsAg in 4%. Although lamivudine monotherapy and combination lamivudine–PEG IFN therapy were both superior to PEG IFN at the end of therapy, no advantage of lamivudine monotherapy or combination therapy was apparent over PEG IFN monotherapy 6 months after therapy—suppression of HBV DNA by a mean of 2.3 $\log_{10}$ copies/mL, undetectable HBV DNA in 19%, and normal ALT in 59%. In subjects involved in this trial followed for up to 5 years, among the two-thirds followed who had been treated initially with PEG IFN, 17% maintained HBV DNA suppression to <400 copies/mL, but ALT remained normal in only 22%; HBsAg loss increased gradually to 12%. Among the half followed who had been treated initially with lamivudine monotherapy, HBV DNA remained <400 copies/mL in 7% and ALT normal in 16%; by year 5, 3.5% had lost HBsAg. As was the case for standard IFN therapy in HBeAg-negative patients, only a small proportion maintained responsiveness after completion of PEG IFN therapy, raising questions about the relative value of a finite period of PEG IFN, versus a longer course with a potent, low-resistance oral nucleoside analogue in these patients. Moreover, the value of PEG IFN for HBeAg-negative chronic hepatitis B has not been confirmed. In the only other controlled clinical trial of PEG IFN for HBeAg-negative chronic hepatitis B, the hepatitis C regimen of PEG IFN plus ribavirin was compared to PEG IFN monotherapy. In this trial, HBV DNA suppression (<400 copies/mL) occurred in only 7.5% of the two groups combined, and no study subject lost HBsAg.

In patients treated with PEG IFN, HBeAg and HBsAg responses have been associated with *IL28B* genotype CC, the favorable genotype identified in trials of PEG IFN for chronic hepatitis C. Also, reductions in quantitative HBsAg levels have been shown to correlate with and to be predictive of responsiveness to PEG IFN in chronic hepatitis B. If HBsAg levels fail to fall within the first 12–24 weeks or to reach <20,000 IU/mL by week 24, PEG IFN therapy is unlikely to be effective and should be discontinued. (Similar observations of HBsAg levels in oral-agent-treated patients are of interest, but of limited clinical relevance, given the very high likelihood of virologic responses during such therapy.)

ENTECAVIR

Entecavir, an oral cyclopentyl guanosine analogue polymerase inhibitor (approved 2005), appears to be the most potent of the HBV antivirals and is just as well tolerated as lamivudine. In a 709-subject clinical trial among HBeAg-reactive patients, oral entecavir, 0.5 mg daily, was compared to lamivudine, 100 mg daily. At 48 weeks, entecavir was superior to lamivudine in suppression of HBV DNA (mean 6.9 vs 5.5 $\log_{10}$ copies/mL), percentage with undetectable HBV DNA (<300 copies/mL by PCR; 67% vs 36%), histologic improvement (≥2-point improvement in necroinflammatory HAI score; 72% vs 62%), and normal ALT (68% vs 60%). The two treatments were indistinguishable in percentage with HBeAg loss (22% vs 20%) and seroconversion (21% vs 18%). Among patients treated with entecavir for 96 weeks, HBV DNA was undetectable cumulatively in 80% (vs 39% for lamivudine), and HBeAg seroconversions had occurred in 31% (vs 26% for lamivudine). After 3–6 years of entecavir, HBeAg seroconversions have been observed in 39–44% and HBsAg loss in 5–6%. Similarly, in a 638-subject clinical trial among HBeAg-negative patients, at week 48, oral entecavir, 0.5 mg daily, was superior to lamivudine, 100 mg daily, in suppression of HBV DNA (mean 5.0 vs 4.5 $\log_{10}$ copies/mL) and in percentage with undetectable HBV DNA (90% vs 72%), histologic improvement (70% vs 61%), and normal ALT (78% vs 71%). No resistance mutations were encountered in previously treatment-naïve, entecavir-treated patients during 96 weeks of therapy, and in a cohort of subjects treated for up to 6 years, resistance emerged in only 1.2%. Entecavir-induced HBeAg seroconversions are as durable as those achieved with other antivirals. Its high barrier to resistance coupled with its high potency renders entecavir a first-line drug for patients with chronic hepatitis B.

Entecavir is also effective against lamivudine-resistant HBV infection. In a trial of 286 lamivudine-resistant patients, entecavir, at a higher daily dose of 1 mg, was superior to lamivudine, as measured at week 48, in achieving suppression of HBV DNA (mean 5.1 vs 0.48 $\log_{10}$ copies/mL), undetectable HBV DNA (72% vs 19%), normal ALT (61% versus 15%), HBeAg loss (10% vs 3%), and HBeAg seroconversion (8% vs 3%). In this population of lamivudine-experienced patients, however, entecavir resistance emerged in 7% at 48 weeks. Although entecavir resistance requires both a YMDD mutation and a second mutation at one of several other sites

(e.g., T184A, S202G/I, or M250V), resistance to entecavir in lamivudine-resistant chronic hepatitis B has been recorded to increase progressively to 43% at 4 years and 57% at 6 years; therefore, entecavir is not as attractive a choice (and is not recommended, despite its approval for this indication) as adefovir or tenofovir for patients with lamivudine-resistant hepatitis B.

In clinical trials, entecavir had an excellent safety profile. In addition, on-treatment and posttreatment ALT flares are relatively uncommon and relatively mild in entecavir-treated patients. Doses should be reduced for patients with reduced creatinine clearance. Entecavir does have low-level antiviral activity against HIV and cannot be used as monotherapy to treat HBV infection in HIV/HBV co-infected persons.

TELBIVUDINE

Telbivudine, a cytosine analogue (approved 2006), is similar in efficacy to entecavir but slightly less potent in suppressing HBV DNA (a slightly less profound median 6.4 $\log_{10}$ reduction in HBeAg-reactive disease and a similar 5.2 $\log_{10}$ reduction in HBeAg-negative disease). In its registration trial, telbivudine at an oral daily dose of 600 mg suppressed HBV DNA to <300 copies/mL in 60% of HBeAg-positive and 88% of HBeAg-negative patients, reduced ALT to normal in 77% of HBeAg-positive and 74% of HBeAg-negative patients, and improved histology in 65% of HBeAg-positive and 67% of HBeAg-negative patients. Although resistance to telbivudine (M204I, not M204V, mutations) was less frequent than resistance to lamivudine at the end of 1 year, resistance mutations after 2 years of treatment occurred in up to 22%. Generally well tolerated, telbivudine has been associated with a low frequency of asymptomatic creatine kinase elevations and with a very low frequency of peripheral neuropathy; frequency of administration should be reduced for patients with impaired creatinine clearance. Its excellent potency notwithstanding, the inferior resistance and safety profile of telbivudine has limited its appeal; telbivudine is neither recommended as first-line therapy nor widely used.

TENOFOVIR

TDF, an acyclic nucleotide analogue and potent antiretroviral agent used to treat HIV infection (approved for hepatitis B in 2008), is similar to adefovir but more potent in suppressing HBV DNA and inducing HBeAg responses; it is highly active against both wild-type and lamivudine-resistant HBV and active in patients whose response to adefovir is slow and/or limited. At an oral once-daily dose of 300 mg for 48 weeks, tenofovir suppressed HBV DNA by 6.2 $\log_{10}$ (to undetectable levels [<400 copies/mL] in 76%) in HBeAg-positive patients and by 4.6 $\log_{10}$ (to undetectable levels in 93%) in HBeAg-negative patients; reduced ALT to normal in 68% of HBeAg-positive and 76% of HBeAg-negative patients; and improved histology in 74% of HBeAg-positive and 72% of HBeAg-negative patients. In HBeAg-positive patients, HBeAg seroconversions occurred in 21% by the end of year 1, 27% by year 2, 34% by year 3, and 40% by year 5 of tenofovir treatment; HBsAg loss occurred in 3% by the end of year 1 and 6% at year 2, and 8% by year 5. After 5 years of tenofovir therapy, 87% of patients experienced histologic improvement, including reduction in fibrosis score (51%) and regression of cirrhosis (71%). The 5-year safety (negligible renal toxicity, in 1%, and mild reduction in bone density, in ~0.5%) and resistance profiles (none recorded through 8 years) of tenofovir are very favorable as well; therefore, tenofovir has supplanted adefovir both as first-line therapy for chronic hepatitis B and as add-on therapy for lamivudine-resistant chronic hepatitis B. Studies of tenofovir and entecavir reviewed in 2015 showed no difference in long-term risks of renal and bone toxicity; however, among patients treated with tenofovir, instances of acute renal failure and of low blood phosphate levels have been reported. Thus, in patients receiving tenofovir, monitoring bone density is not recommended, but periodic (at least annual) monitoring for renal injury is (serum creatinine and phosphate, urine glucose and protein). Frequency of tenofovir administration should be reduced for patients with impaired creatinine clearance.

A comparison of the six antiviral therapies in current use appears in Table 334-3; their relative potencies in suppressing HBV DNA are shown in Fig. 334-1.

COMBINATION THERAPY

Although the combination of lamivudine and PEG IFN suppresses HBV DNA more profoundly during therapy than does monotherapy with either drug alone (and is much less likely to be associated with lamivudine resistance), this combination used for a year is no better than a year of PEG IFN in achieving sustained responses. To date, combinations of oral nucleoside/nucleotide agents have not achieved an enhancement in virologic, serologic, or biochemical efficacy over that achieved by the more potent of the combined drugs given individually. In a 2-year trial of combination entecavir and tenofovir versus entecavir monotherapy, for a small subgroup of patients with very high HBV DNA levels ($\geq 10^8$ IU/mL), a reduction in HBV DNA to <50 IU/mL was higher in the combination group (79% vs 62%); however, no differences in HBeAg responses or any other endpoint were observed between the combination-therapy and monotherapy groups, even in the high-HBV DNA subgroup. On the other hand, combining agents that are not cross-resistant (e.g., lamivudine or entecavir with adefovir or tenofovir) has the potential to reduce the risk or perhaps even to preempt entirely the emergence of drug resistance. In the future, the treatment paradigm may shift from the current approach of sequential monotherapy to preemptive combination therapy, perhaps not for all patients but for subsets (e.g., patients with very high levels of HBV DNA, immunosuppressed patients); however, designing and executing clinical trials that demonstrate superior efficacy and resistance profile of combination therapy over monotherapy with entecavir or tenofovir will remain challenging. Whereas, initially, in clinical studies of adefovir as rescue therapy for lamividune resistance, *adding* adefovir to lamivudine (combination therapy) was considered a better strategy than replacing lamivudine with adefovir monotherapy, according to the 2016 treatment recommendations of the American Association for the Study of Liver Diseases (AASLD), data to support adding or switching agents are insufficient. Therefore, while sound virologic principles would favor adding as opposed to switching, according to current recommendations involving the more potent first-line agents, entecavir for tenofovir resistance and tenofovir for entecavir resistance, either strategy is acceptable. For patients who already have acquired multidrug resistance (to both nucleoside analogues [lamivudine, entecavir, telbivudine] and nucleotide analogues [adefovir, tenofovir]), treatment with a combination of entecavir and tenofovir has been shown to be highly effective in suppressive HBV DNA and overcoming drug resistance.

NOVEL ANTIVIRALS AND STRATEGIES

In addition to the seven approved antiviral drugs for hepatitis B, emtricitabine, a fluorinated cytosine analogue very similar to lamivudine in structure, efficacy, and resistance profile, offers no advantage over lamivudine. A combination of emtricitabine and tenofovir is approved for the treatment of HIV infection and is an appealing combination therapy for hepatitis B, especially for lamivudine-resistant disease; however, neither emtricitabine nor the combination is approved for hepatitis B. Several initially promising antiviral agents have been abandoned because of toxicity (e.g., clevudine, which was linked to myopathy during its clinical development). As noted above, the current formulation of tenofovir, TDF, has been associated with renal toxicity and loss of bone density, especially in patients with HIV infection, less so in patients with HBV infection. A new formulation, tenofovir alafenamide (TAF), is a prodrug of tenofovir that is metabolized to the active agent in its target organ (the liver for HBV infection); such targeting permits higher dose delivery to the liver with markedly reduced systemic exposure. Studies in patients with chronic hepatitis B treated with 25 mg of TAF or 300 mg of TDF demonstrate comparable virologic efficacy as well as less reduction in bone mineral density and estimated glomerular filtration rate for TAF. Based on its better renal and bone safety profile than TDF, TAF has been approved for HBV infection

TABLE 334-3 Comparison of Pegylated Interferon (PEG IFN), Lamivudine, Adefovir, Entecavir, Telbivudine, and Tenofovir Therapy for Chronic Hepatitis B[a]

FEATURE	PEG IFN[b]	LAMIVUDINE	ADEFOVIR	ENTECAVIR	TELBIVUDINE	TENOFOVIR
Route of administration	Subcutaneous injection	Oral	Oral	Oral	Oral	Oral
Duration of therapy[c]	48–52 weeks	≥52 weeks	≥48 weeks	≥48 weeks	≥52 weeks	≥48 weeks
Tolerability	Poorly tolerated	Well tolerated	Well tolerated; creatinine monitoring recommended	Well tolerated	Well tolerated	Well tolerated; creatinine monitoring recommended
HBeAg seroconversion						
1 yr Rx	18–20%	16–21%	12%	21%	22%	21%
>1 yr Rx	NA	up to 50% @ 5 yrs	43% @ 3 yrs[d]	31% @ 2 yrs 44% @ 6 yrs	30% @ 2 yrs	40% @ 5 yrs
Log_{10} HBV DNA reduction (mean copies/mL)						
HBeAg-reactive	4.5	5.5	median 3.5–5	6.9	6.4	6.2
HBeAg-negative	4.1	4.4–4.7	median 3.5–3.9	5.0	5.2	4.6
HBV DNA PCR negative (<300–400 copies/mL; <1000 copies/mL for adefovir) at end of yr 1						
HBeAg-reactive	10–25%	36–44%	13–21%	67% (91% @ 4 yrs)	60%	76%
HBeAg-negative	63%	60–73%	48–77%	90%	88%	93%
ALT normalization at end of yr 1						
HBeAg-reactive	39%	41–75%	48–61%	68%	77%	68%
HBeAg-negative	34–38%	62–79%	48–77%	78%	74%	76%
HBsAg loss yr 1	3–4%	≤1%	0%	2%	<1%	3%
>yr 1	12% 5 yr after 1 yr of Rx	No data	5% at yr 5	6% at yr 6	No data	8% at yr 5
Histologic improvement (≥2 point reduction in HAI) at yr 1						
HBeAg-reactive	38% 6 months after	49–62%	53–68%	72%	65%	74%
HBeAg-negative	48% 6 months after	61–66%	64%	70%	67%	72%
Viral resistance	None	15–30% @ 1 yr 70% @ 5 yrs	None @ 1 yr 29% @ 5 yrs	≤1% @ 1 yr[e] 1.2% @ 6 yrs[e]	Up to 5% @ yr 1 Up to 22% @ yr 2	0% @ yr 1 0% through yr 8
Pregnancy category	C	C[f]	C	C	B	B
Cost (US$) for 1 yr	~$18,000	~$2,500	~$6,500	~$8,700[g]	~$6,000	~$6,000

[a]Generally, these comparisons are based on data on each drug tested individually versus placebo in registration clinical trials; because, with rare exception, these comparisons are not based on head-to-head testing of these drugs, relative advantages and disadvantages should be interpreted cautiously. [b]Although standard interferon α administered daily or three times a week is approved as therapy for chronic hepatitis B, it has been supplanted by PEG IFN, which is administered once a week and is more effective. Standard interferon has no advantages over PEG IFN. [c]Duration of therapy in clinical efficacy trials; use in clinical practice may vary. [d]Because of a computer-generated randomization error that resulted in misallocation of drug versus placebo during the second year of clinical trial treatment, the frequency of HBeAg seroconversion beyond the first year is an estimate (Kaplan-Meier analysis) based on the small subset in whom adefovir was administered correctly. [e]7% during a year of therapy (43% at year 4) in lamivudine-resistant patients. [f]Despite its Class C designation, lamivudine has an extensive pregnancy safety record in women with HIV/AIDS. [g]Approximately $17,400 for lamivudine-refractory patients.

Abbreviations: ALT, alanine aminotransferase; HAI, histologic activity index; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; NA, not applicable; PEG IFN, pegylated interferon; PCR, polymerase chain reaction; Rx, therapy; yr, year.

and provides an alternative to TDF in patients with TDF-associated elevations in serum creatinine and/or reductions in serum phosphorus. Direct-acting antivirals (DAAs) have been very successful in the management of chronic hepatitis B; however, most patients require long-duration, usually indefinite, therapy. Ideally, an approach to achieving "cure" (eradication of HBV infection) with finite-duration therapy would be welcome. Currently, innovative approaches being investigated include viral entry inhibitors, nucleocapsid assembly inhibitors, HBV secretion (HBsAg release) inhibitors, immunomodulators (e.g., toll receptor agonists, T-cell vaccines, programmed cell death [PD-1] blockade, reconstitution of innate and adaptive immune responses, HBV mRNA recognition and activation of innate immune signaling by retinoic acid-inducible gene-I [RIG-I]), covalently closed circular (ccc) DNA silencing/inhibition/cleavage, RNA interference, and HBx inhibitors. While data supporting several of these unconventional approaches have begun to appear, none has been shown to "cure" hepatitis B, and none is likely to be competitive, unless it can be shown to go beyond current antivirals in achieving recovery (HBsAg seroconversion) from HBV infection. Finally, initial emphasis in the development of antiviral therapy for hepatitis B was placed on monotherapy; whether combination regimens will yield additive or synergistic efficacy remains to be determined.

TREATMENT RECOMMENDATIONS

Several learned societies and groups of expert physicians have issued treatment recommendations for patients with chronic hepatitis B; the most authoritative and updated (and free of financial support by pharmaceutical companies) are those of the AASLD and of the European Association for the Study of the Liver (EASL). Although the recommendations differ slightly, a consensus has emerged on most of the important points **(Table 334-4)**. No treatment is recommended or available for inactive "nonreplicative" hepatitis B carriers (undetectable HBeAg with normal ALT and HBV

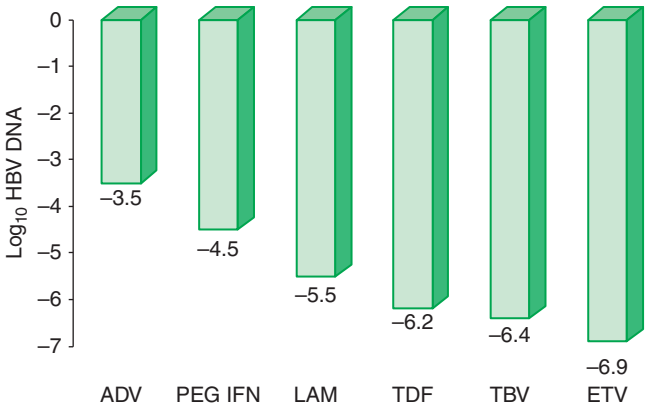

FIGURE 334-1 Relative potency of antiviral drugs for hepatitis B, as reflected by median $\log_{10}$ HBV DNA reduction in HBeAg-positive chronic hepatitis B. These data are from individual reports of large, randomized controlled registration trials that were the basis for approval of the drugs. In most instances, these data do not represent direct comparisons among the drugs, because study populations were different, baseline patient variables were not always uniform, and the sensitivity and dynamic range of the HBV DNA assays used in the trials varied. ADV, adefovir dipivoxil; ETV, entecavir; LAM, lamivudine; PEG IFN, pegylated interferon α2a; TBV, telbivudine; TDF, tenofovir disoproxil fumarate.

DNA ≤10^3 IU/mL documented serially over time). In patients with detectable HBeAg and HBV DNA levels >2 × 10^4 IU/mL, treatment is recommended by the AASLD for those with ALT levels above 2 × the upper limit of normal. (The EASL recommends treatment in HBeAg-positive patients for HBV DNA levels >2 × 10^3 IU/mL and ALT above the upper limit of normal.) For HBeAg-positive patients with ALT ≤2 × the upper limit of normal, in whom sustained responses are not likely and who would require multiyear therapy, antiviral therapy is not recommended currently. This pattern is common during the early decades of life among Asian patients infected at birth; even in this group, therapy would be considered for those >40 years of age, ALT persistently at the high end of the twofold range, and/or with a family history of HCC, especially if the liver biopsy shows moderate to severe necroinflammatory activity or fibrosis. In this group, when, eventually, ALT becomes elevated later in life, antiviral therapy should be instituted. For patients with HBeAg-negative chronic hepatitis B, ALT >2 × the upper limit of normal (above the upper limit of normal according to EASL), and HBV DNA >2 × 10^3 IU/mL, antiviral therapy is recommended. If HBV DNA is >2 × 10^3 IU/mL and ALT is 1 to >2 × the upper limit of normal, liver biopsy should be considered to help in arriving at a decision to treat if substantial liver injury is present (treatment in this subset would be recommended according to EASL guidelines, because ALT is elevated). Per current AASLD recommendations, antiviral treatment with oral agents can be stopped after HBeAg seroconversion in noncirrhotics, and the suggested period of consolidation therapy is 12 months with close monitoring for recurrent viremia (monthly × 6, then every 3 months for the rest of a year) after cessation of therapy. For patients with HBeAg-negative chronic hepatitis, the current recommendation with oral agents is for indefinite therapy; although sufficient data are lacking, stopping therapy in this group can be considered after HBsAg loss.

For patients with compensated cirrhosis, because antiviral therapy has been shown to retard clinical progression, treatment is recommended regardless of HBeAg status and ALT as long as HBV DNA is detectable at >2 × 10^3 IU/mL (detectable at any level according to the EASL); monitoring without therapy is recommended for those with HBV DNA <2 × 10^3 IU/mL, unless ALT is elevated. For patients with decompensated cirrhosis, treatment is recommended regardless of serologic and biochemical status, as long as HBV DNA is detectable. Patients with decompensated cirrhosis should be evaluated as candidates for liver transplantation.

Among the seven available drugs for hepatitis B, PEG IFN has supplanted standard IFN, entecavir has supplanted lamivudine, and tenofovir has supplanted adefovir. PEG IFN, entecavir, or tenofovir is recommended as first-line therapy (Table 334-3). PEG

TABLE 334-4 Recommendations for Treatment of Chronic Hepatitis B[a]

HBeAg STATUS	CLINICAL	HBV DNA (IU/mL)	ALT	RECOMMENDATION
HBeAg-reactive	[b]	>2 × 10^4	≤2 × ULN[c,d]	No treatment; monitor. In patients >40, with family history of hepatocellular carcinoma, and/or ALT persistently at the high end of the twofold range, liver biopsy may help in decision to treat
	Chronic hepatitis	>2 × 10^4[d]	>2 × ULN[d]	Treat[e]
	Cirrhosis compensated	>2 × 10^3	< or > ULN	Treat[e] with oral agents, not PEG IFN
	Cirrhosis decompensated	<2 × 10^3	>ULN	Consider treatment[f]
		Detectable	< or > ULN	Treat[e] with oral agents[g], not PEG IFN; refer for liver transplantation
		Undetectable	< or > ULN	Observe; refer for liver transplantation
HBeAg-negative	[b]	≤2 × 10^3	≤ULN	Inactive carrier; treatment not necessary
	Chronic hepatitis	>10^3	1 to >2 × ULN[d]	Consider liver biopsy; treat[h] if biopsy shows moderate to severe inflammation or fibrosis
	Chronic hepatitis	>10^4	>2 × ULN[d]	Treat[h,i]
	Cirrhosis compensated	>2 × 10^3	< or > ULN	Treat[e] with oral agents, not PEG IFN
		<2 × 10^3	>ULN	Consider treatment[f]
	Cirrhosis decompensated	Detectable	< or > ULN	Treat[h] with oral agents[g], not PEG IFN; refer for liver transplantation
		Undetectable	< or > ULN	Observe; refer for liver transplantation

[a]Based on practice guidelines of the American Association for the Study of Liver Diseases (AASLD). Except as indicated in footnotes, these guidelines are similar to those issued by the European Association for the Study of the Liver (EASL). [b]Liver disease tends to be mild or inactive clinically; most such patients do not undergo liver biopsy. [c]This pattern is common during early decades of life in Asian patients infected at birth. [d]According to the EASL guidelines, treat if HBV DNA is >2 × 10^3 IU/mL and ALT >ULN. [e]One of the potent oral drugs with a high barrier to resistance (entecavir or tenofovir) or PEG IFN can be used as first-line therapy (see text). These oral agents, but not PEG IFN, should be used for interferon-refractory/intolerant and immunocompromised patients. PEG IFN is administered weekly by subcutaneous injection for a year; the oral agents are administered daily for at least a year and continued indefinitely or until at least 6 months after HBeAg seroconversion. [f]According to EASL guidelines, patients with compensated cirrhosis and detectable HBV DNA at any level, even with normal ALT, are candidates for therapy. Most authorities would treat indefinitely, even in HBeAg-positive disease after HBeAg seroconversion. [g]Because the emergence of resistance can lead to loss of antiviral benefit and further deterioration in decompensated cirrhosis, a low-resistance regimen is recommended—entecavir or tenofovir monotherapy or combination therapy with the more resistance-prone lamivudine (or telbivudine) plus adefovir. Therapy should be instituted urgently. [h]Because HBeAg seroconversion is not an option, the goal of therapy is to suppress HBV DNA and maintain a normal ALT. PEG IFN is administered by subcutaneous injection weekly for a year; caution is warranted in relying on a 6-month posttreatment interval to define a sustained response, because the majority of such responses are lost thereafter. Oral agents, entecavir or tenofovir, are administered daily, usually indefinitely or until, as very rarely occurs, virologic and biochemical responses are accompanied by HBsAg seroconversion. [i]For older patients and those with advanced fibrosis, consider lowering the HBV DNA threshold to >2 × 10^3 IU/mL.

Abbreviations: AASLD, American Association for the Study of Liver Diseases; ALT, alanine aminotransferase; EASL, European Association for the Study of the Liver; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; PEG IFN, pegylated interferon; ULN, upper limit of normal.

IFN requires finite-duration therapy, achieves the highest rate of HBeAg responses after a year of therapy, and does not support viral mutations, but it requires subcutaneous injections and is associated with inconvenience, more intensive clinical and laboratory monitoring, and intolerability. Oral nucleoside analogues require long-term therapy in most patients, and when used alone, lamivudine and telbivudine foster the emergence of viral mutations, adefovir somewhat less so, and entecavir (except in lamivudine-experienced patients) and tenofovir rarely at all. Oral agents do not require injections or cumbersome laboratory monitoring, are very well tolerated, lead to improved histology in 50–90% of patients, suppress HBV DNA more profoundly than PEG IFN, and are effective even in patients who fail to respond to IFN-based therapy. Although oral agents are less likely to result in HBeAg responses during the first year of therapy, as compared to PEG IFN, treatment with oral agents tends to be extended beyond the first year and, by the end of the second year, yields HBeAg responses (and even HBsAg responses) comparable in frequency to those achieved after 1 year of PEG IFN (and without the associated side effects) **(Table 334-5)**. In a 2016 systematic review of 1716 patients involved in 25 clinical trials, responses after oral-agent therapy were found to be durable. Among patients with HBeAg-reactive chronic hepatitis B, the pooled rates of durable HBeAg seroconversions maintained after cessation of nucleoside/nucleotide analogue therapy (including all the oral agents) were 92% and 88% at posttreatment months 12 and 24, respectively, unaffected by the duration of post-HBeAg-response consolidation therapy (>6 months in all studies evaluated); the pooled rate of durable biochemical remission after therapy in this population was 76%. Even for HBeAg-negative chronic hepatitis B, for which most authorities recommend indefinite therapy, pooled rates of virologic remissions maintained after cessation of oral-agent therapy were 44%, 31%, and 30% at posttreatment months 12, 24, and 36, and the pooled rate of durable biochemical remission in this population was 57%.

TABLE 334-5 Pegylated Interferon Versus Oral Nucleoside Analogues for the Treatment of Chronic Hepatitis B

	PEG IFN	NUCLEOSIDE ANALOGUES
Administration	Weekly injection	Daily, orally
Tolerability	Poorly tolerated, intensive monitoring	Well tolerated, limited monitoring
Duration of therapy	Finite 48 weeks	≥1 year, indefinite in most patients
Maximum mean HBV DNA suppression	4.5 $\log_{10}$	6.9 $\log_{10}$
Effective in high-level HBV DNA ($\geq 10^9$ IU/mL)	No	Yes
HBeAg seroconversion		
During 1 year of therapy	~30%	~20%
During >1 year of therapy	Not applicable	30% (year 2) to up to 50% (year 5)
HBeAg-negative posttreatment HBV DNA suppression	17% @ 5 years	7% @ 4 years (lamivudine)
HBsAg loss		
During 1 year of therapy	3–4%	0–3%
During >1 year of therapy	Not applicable	3–8% @ 5 years of therapy
After 1 year of therapy–HBeAg-negative	12% @ 5 years	3.5% @ 5 years
Antiviral resistance	None	Lamivudine: ~30% year 1, ~70% year 5 Adefovir: 0% year 1, ~30% year 5 Telbivudine: up to 4% year 1, 22% year 2 Entecavir: ≤1.2% through year 6 Tenofovir: 0% through year 8
Use in cirrhosis, transplantation, immunosuppressed	No	Yes
Cost, 1 year of therapy	++++	+ to ++

Abbreviations: HBV, hepatitis B virus; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; PEG IFN, pegylated interferon.

Although adefovir and tenofovir are safe, renal monitoring (e.g., serum creatinine and phosphate, urine glucose and protein) is recommended. Substantial experience with lamivudine during pregnancy (see above) has identified no teratogenicity; although widely used during pregnancy, lamivudine remains classified as pregnancy category C. Although IFNs do not appear to cause congenital anomalies, these have antiproliferative properties and should be avoided during pregnancy. Adefovir during pregnancy has not been associated with birth defects; however, the risk of spontaneous abortion may be increased, and adefovir is categorized as pregnancy category C. Data on the safety of entecavir during pregnancy have not been published (pregnancy category C). Sufficient data in animals and limited data in humans suggest that telbivudine and tenofovir (both pregnancy category B) can be used safely during pregnancy; however, telbivudine is not an acceptable first-line drug. In general, then, except for lamivudine and tenofovir, and until additional data become available, the other antivirals for hepatitis B should be avoided or used with extreme caution during pregnancy.

For children aged 2 to <18 with HBeAg-reactive hepatitis B (most children will be HBeAg-reactive; no studies have been done in children with HBeAg-negative chronic hepatitis B), treatment is recommended if HBV DNA is detectable and ALT levels are elevated, but not if ALT levels are normal. Each of the available drugs, except telbivudine, is approved for different childhood age groups (standard IFN α-2b age ≥1 year; PEG IFN α-2a age ≥5 years [approved for hepatitis C, not B, but can be used in hepatitis B]; lamivudine and entecavir age ≥2 years; adefovir and tenofovir age ≥12 years). Package inserts should be consulted for childhood doses.

As noted above, some physicians prefer to begin with PEG IFN, while other physicians and patients prefer oral agents as first-line therapy. For patients with decompensated cirrhosis, the emergence of resistance can result in further deterioration and loss of antiviral effectiveness. Therefore, in this patient subset, the threshold for relying on therapy with a very favorable resistance profile (e.g., entecavir or tenofovir) or on combination therapy is low. PEG IFN should not be used in patients with compensated or decompensated cirrhosis.

For patients with end-stage chronic hepatitis B who undergo liver transplantation, reinfection of the new liver is almost universal in the absence of antiviral therapy. The majority of patients become high-level viremic carriers with minimal liver injury. Before the availability of antiviral therapy, an unpredictable proportion experienced severe hepatitis B–related liver injury, sometimes a fulminant-like hepatitis and sometimes a rapid recapitulation of the original severe chronic hepatitis B **(Chap. 332)**. Currently, however, prevention of recurrent hepatitis B after liver transplantation has been achieved definitively by *combining* hepatitis B immune globulin with one of the low-resistance oral nucleoside (entecavir) or nucleotide analogues (tenofovir) **(Chap. 338)**; preliminary data suggest that the newer, more potent, and less resistance-prone oral agents may be used instead of hepatitis B immune globulin for posttransplantation therapy. In patients documented at the time of liver transplantation to have undetectable HBV DNA in serum and cccDNA in the liver (i.e., with low risk for recurrence of HBV infection), a preliminary clinical trial suggested that, after patients received 5 years of combined therapy, both hepatitis B immune globulin and oral-agent therapy can be withdrawn sequentially (over two 6-month periods) with a success rate, as monitored over a median of 6 years postwithdrawal, of 90% and an anti-HBs seroconversion rate of 60% (some with transient reappearance of HBV DNA and/or HBsAg).

Patients with HBV-HIV co-infection can have progressive HBV-associated liver disease and, occasionally, a severe exacerbation of hepatitis B resulting from immunologic reconstitution following

ART. Lamivudine should never be used as monotherapy in patients with HBV-HIV infection because HIV resistance emerges rapidly to both viruses. Adefovir has been used successfully to treat chronic hepatitis B in HBV-HIV co-infected patients but is no longer considered a first-line agent for HBV. Entecavir has low-level activity against HIV and can result in selection of HIV resistance; therefore, it should be avoided in HBV-HIV co-infection. Tenofovir and the combination of tenofovir and emtricitabine in one pill are approved therapies for HIV and represent excellent choices for treating HBV infection in HBV-HIV co-infected patients. Generally, even for HBV-HIV co-infected patients who do not yet meet treatment criteria for HIV infection, treating for both HBV and HIV is recommended.

Patients with chronic hepatitis B who undergo cytotoxic chemotherapy for treatment of malignancies as well as patients treated with immunosuppressive, anticytokine, or antitumor necrosis factor therapies (the risk varies, from highest [e.g., B-cell-depleting agents, anthracycline derivatives, moderate/high-dose corticosteroids for ≥4 weeks] to moderate [e.g., tumor necrosis factor alpha inhibitors, cytokine or integrin inhibitors, tyrosine kinase inhibitors, low-dose corticosteroids for ≥4 weeks], to lowest [e.g., immunosuppressive agents like methotrexate and azathioprine, intraarticular corticosteroids, any dose of corticosteroids for ≤1 week]) experience enhanced HBV replication and viral expression on hepatocyte membranes during chemotherapy coupled with suppression of cellular immunity. When chemotherapy is withdrawn, such patients are at risk for reactivation of hepatitis B, often severe and occasionally fatal. Such rebound reactivation represents restoration of cytolytic T cell function against a target organ enriched in HBV expression. Preemptive treatment with the first of the oral HBV antivirals, lamivudine, prior to the initiation of chemotherapy was shown to reduce the risk of such reactivation substantially; treating *after* reactivation has occurred is less effective. The newer, more potent oral antiviral agents, entecavir and tenofovir, which are even more effective in preventing hepatitis B reactivation and with a lower risk of antiviral drug resistance, are preferred. The optimal duration of antiviral therapy after completion of chemotherapy is not known, but a suggested approach is 6 months (12 months for B-cell-depleting agents) for inactive hepatitis B carriers and longer-duration therapy in patients with baseline HBV DNA levels $>2 \times 10^3$ IU/mL, until standard clinical endpoints are met (Table 334-4). Such chemotherapy-associated reactivation of hepatitis B is common (4–68%, median 25%, in a meta-analysis) in persons with ongoing HBV infection (HBsAg-reactive); however, such reactivation can occur albeit less commonly in persons who have cleared HBsAg, but express anti-HBc (moderate risk, <10%) and rarely (<5%) even in persons with serologic evidence of recovery from HBV infection (anti-HBs-reactive, anti-HBc-reactive). Therefore, most authorities (e.g., Centers for Disease Control and Prevention; AASLD; American Gastroenterological Association; EASL) recommend HBsAg and anti-HBc (± anti-HBs) screening of all patients undergoing such chemotherapy and preemptive antiviral prophylaxis for HBsAg-reactive persons and close on-therapy monitoring of anti-HBc-reactive/anti-HBs-reactive persons with treatment if and when reactivation occurs.

CHRONIC HEPATITIS D (DELTA HEPATITIS)

Chronic hepatitis D virus (HDV) may follow acute co-infection with HBV but at a rate no higher than the rate of chronicity of acute hepatitis B. That is, although HDV co-infection can increase the severity of acute hepatitis B, HDV does not increase the likelihood of progression to chronic hepatitis B. When, however, HDV superinfection occurs in a person who is already chronically infected with HBV, long-term HDV infection is the rule, and a worsening of the liver disease is the expected consequence. Except for severity, chronic hepatitis B plus D has similar clinical and laboratory features to those seen in chronic hepatitis B alone. Relatively severe and progressive chronic hepatitis, with or without cirrhosis, is the rule, and mild chronic hepatitis is the exception. Occasionally, however, mild hepatitis or even, rarely, inactive carriage occurs in patients with chronic hepatitis B plus D, and the disease may become indolent after several years of infection. A distinguishing serologic feature of chronic hepatitis D is the presence in the circulation of antibodies to liver-kidney microsomes (anti-LKM); however, the anti-LKM seen in hepatitis D, anti-LKM3, are directed against uridine diphosphate glucuronosyltransferase and are distinct from anti-LKM1 seen in patients with autoimmune hepatitis and in a subset of patients with chronic hepatitis C (see below). **The clinical and laboratory features of chronic HDV infection are summarized in Chap. 332.**

TREATMENT

Chronic Hepatitis D

Management is not well defined, and the host cellular RNA polymerase upon which HDV replication depends cannot be targeted by conventional antiviral agents. Glucocorticoids are ineffective and are not used. Preliminary experimental trials of IFN-α suggested that conventional doses and durations of therapy lower levels of HDV RNA and aminotransferase activity only transiently during treatment but have no impact on the natural history of the disease. In contrast, high-dose IFN-α (9 million units three times a week) for 12 months was reported to be associated with a sustained loss of HDV replication and clinical improvement in up to 50% of patients. Moreover, in anecdotal reports, the beneficial impact of treatment has been observed to persist for 15 years and to be associated with a reduction in grade of hepatic necrosis and inflammation, reversion of advanced fibrosis (improved stage), and clearance of HDV RNA in some patients. A suggested approach to therapy has been high-dose, long-term IFN for at least a year and, in responders, extension of therapy until HDV RNA and HBsAg clearance; however, extension of therapy to a second year provided no advantage, and sustained responses after completion of therapy have been rare. PEG IFN has also been shown to be more effective in the treatment of chronic hepatitis D (e.g., after 48 weeks of therapy, associated with undetectable HDV RNA, durable for at least 24 posttreatment weeks, in a quarter to a half of patients) and is a more convenient replacement for standard IFN; however, loss of virologic responses (reappearance of HDV RNA) was observed during long-term (median 4.5-year) monitoring in over half of initial, 24-week-post-treatment responders. Even extending PEG IFN therapy for 5 years and driving treatment doses up to 270 μg weekly (of PEG IFN- α2a), as reported in a small trial among 13 patients, while achieving serologic, virologic, histologic, biochemical, and clinical improvement, yielded sustained virologic responses (SVRs) in only 3 patients (58–246 weeks of posttreatment observation). None of the nucleoside analogue antiviral agents for hepatitis B is effective in hepatitis D, and adding oral nucleoside agents to PEG IFN is no more effective than PEG IFN monotherapy. While recommended, PEG IFN therapy is far from satisfactory. Preliminary trials have been performed with an oral prenylation inhibitor, lonafarnib, and with an inhibitor of HBV/HDV viral entry into hepatocytes, myrcludex B. Prenylation, the posttranslational covalent addition of the prenyl lipid farnesyl to large HDV antigen, is required for this HDV protein to interact and form secreted viral particles with HBsAg. In 14 patients treated twice daily for 28 days with 100 or 200 mg of lonafarnib, HDV RNA fell by 0.73 $\log_{10}$ IU/mL and 1.54 $\log_{10}$ IU/mL, respectively, before rebounding after completion of therapy. Hepatitis B virus entry into hepatocytes requires the binding of the myristolated N-terminal pre-S1 peptide of large HBsAg to sodium taurocholate co-transporting peptide, the functional receptor for HBV into hepatocytes. The application of myrcludex B, a synthetic homologous myristolated lipopeptide that competes for binding with HBsAg, was reported in a study of 24 patients (with a baseline mean of 4.1–4.2 $\log_{10}$ copies/mL of HDV RNA) randomized to 24 weeks of treatment with myrcludex B (2 mg daily subcutaneously) as monotherapy or combined with PEG IFN compared to PEG IFN alone. A reduction in HDV RNA occurred in all three groups, by 1.67 $\log_{10}$ copies/mL (in two of eight patients RNA became undetectable), 2.59 $\log_{10}$ copies/mL (in five of eight patients RNA became undetectable), and 2.17 $\log_{10}$ copies/mL

(in two of eight patients RNA became undetectable), respectively. No change occurred, however, in the level of HBsAg, which would have been expected. In these two exploratory brief-duration trials, sustained responses were not achieved, and toxicities were encountered (e.g., intermittent vomiting and weight loss [lonafarnib] and transient amylase and lipase elevations [myrcludex B]); however, from these proof-of-principle trials, potentially, more definitive and larger-scale studies will follow.

In patients with end-stage liver disease secondary to chronic hepatitis D, liver transplantation has been effective. If hepatitis D recurs in the new liver without the expression of hepatitis B (an unusual serologic profile in immunocompetent persons but common in transplant patients), liver injury is limited. In fact, the outcome of transplantation for chronic hepatitis D is superior to that for chronic hepatitis B; in such patients, combination hepatitis B immune globulin and nucleoside analogue therapy for hepatitis B is indicated **(Chap. 338)**.

CHRONIC HEPATITIS C

Regardless of the epidemiologic mode of acquisition of hepatitis C virus (HCV) infection, chronic hepatitis follows acute hepatitis C in 50–70% of cases; chronic infection is common even in those with a return to normal in aminotransferase levels after acute hepatitis C, adding up to an 85% likelihood of chronic HCV infection after acute hepatitis C. Few clues had emerged to explain host differences associated with chronic infection until recently, when variation in a single nucleotide polymorphism (SNP) on chromosome 19, *IL28B* (which codes for IFN-λ3), was identified that distinguished between responders and nonresponders to IFN-based antiviral therapy (see below). The same variants correlated with spontaneous resolution after acute infection: 53% in genotype C/C, 30% in genotype C/T, but only 23% in genotype T/T. The association with HCV clearance after acute infection is even stronger when *IL28B* haplotype is combined with haplotype G/G of a SNP near human leukocyte antigen (HLA) Class II *DBQ1*03:01*.

In patients with chronic hepatitis C followed for 20 years, progression to cirrhosis occurs in about 20–25%. Such is the case even for patients with relatively clinically mild chronic hepatitis, including those without symptoms, with only modest elevations of aminotransferase activity, and with mild chronic hepatitis on liver biopsy. Even in cohorts of well compensated patients with chronic hepatitis C referred for clinical research trials (no complications of chronic liver disease and with normal hepatic synthetic function), the prevalence of cirrhosis may be as high as 50%. Most cases of hepatitis C are identified initially in asymptomatic patients who have no history of acute hepatitis C (e.g., those discovered while attempting to donate blood, while undergoing lab testing as part of an application for life insurance, or as a result of routine laboratory tests). The source of HCV infection in many of these cases is not defined, although a long-forgotten percutaneous exposure (e.g., injection drug use) in the remote past can be elicited in a substantial proportion and probably accounts for most infections; most of these infections were acquired in the 1960s and 1970s, coming to clinical attention decades later.

Approximately one-third of patients with chronic hepatitis C have normal or near-normal aminotransferase activity; although one-third to one-half of these patients have chronic hepatitis on liver biopsy, the grade of liver injury and stage of fibrosis tend to be mild in the vast majority. In some cases, more severe liver injury has been reported—even, rarely, cirrhosis, most likely the result of previous histologic activity. Among patients with persistent normal aminotransferase activity sustained over ≥5–10 years, histologic progression has been shown to be rare; however, approximately one-fourth of patients with normal aminotransferase activity experience subsequent aminotransferase elevations, and histologic injury can be progressive once abnormal biochemical activity resumes. Therefore, continued clinical monitoring and antiviral therapy are indicated, even for patients with normal aminotransferase activity.

Despite this substantial rate of progression of chronic hepatitis C, and despite the fact that liver failure can result from end-stage chronic hepatitis C, the long-term prognosis over 1–2 decades for chronic hepatitis C in a majority of patients is relatively benign. Mortality >10–20 years among patients with transfusion-associated chronic hepatitis C has been shown not to differ from mortality in a matched population of transfused patients in whom hepatitis C did not develop. Although death in the hepatitis group is more likely to result from liver failure, and although hepatic decompensation may occur in ~15% of such patients over the course of a decade, the majority (almost 60%) of patients remain asymptomatic and well compensated, with no clinical sequelae of chronic liver disease. Overall, chronic hepatitis C tends to be very slowly and insidiously progressive, if at all, in the vast majority of patients, whereas in approximately one-fourth of cases, chronic hepatitis C will progress eventually to end-stage cirrhosis. In fact, because HCV infection is so prevalent, and because a proportion of patients progress inexorably to end-stage liver disease, hepatitis C is the most frequent indication for liver transplantation **(Chap. 338)**. In the United States, hepatitis C accounts for up to 40% of all chronic liver disease; as of 2007, mortality caused by hepatitis C surpassed that associated with HIV/AIDS, and as of 2012, reported deaths caused by hepatitis C surpassed those associated with all other notifiable infectious diseases (HIV, tuberculosis, hepatitis B, and 57 other infectious diseases). Moreover, because the prevalence of HCV infection is so much higher in the "baby boomer" cohort born between 1945 and 1965, three-quarters of the mortality associated with hepatitis C occurs in this age cohort. Referral bias may account for the more severe outcomes described in cohorts of patients reported from tertiary care centers (20-year progression of ≥20%) versus the more benign outcomes in cohorts of patients monitored from initial blood-product-associated acute hepatitis or identified in community settings (20-year progression of only 4–7%). Still unexplained, however, are the wide ranges in reported progression to cirrhosis, from 2% over 17 years in a population of Irish women with hepatitis C infection acquired from contaminated anti-D immune globulin to 30% over ≤11 years in recipients of contaminated intravenous immune globulin.

Progression of liver disease in patients with chronic hepatitis C has been reported to be more likely in patients with older age, longer duration of infection, advanced histologic stage and grade, more complex HCV quasispecies diversity, increased hepatic iron, concomitant other liver disorders (alcoholic liver disease, chronic hepatitis B, hemochromatosis, α_1 antitrypsin deficiency, and steatohepatitis), HIV infection, and obesity. Among these variables, however, duration of infection appears to be one of the most important, and some of the others probably reflect disease duration to some extent (e.g., quasispecies diversity, hepatic iron accumulation). No other epidemiologic or clinical features of chronic hepatitis C (e.g., severity of acute hepatitis, level of aminotransferase activity, level of HCV RNA, presence or absence of jaundice during acute hepatitis) are predictive of eventual outcome. Despite the relatively benign nature of chronic hepatitis C over time in many patients, cirrhosis following chronic hepatitis C has been associated with the late development, after several decades, of HCC **(Chap. 78)**; the annual rate of HCC in cirrhotic patients with hepatitis C is 1–4%, occurring primarily in patients who have had HCV infection for 30 years or more.

Perhaps the best prognostic indicator in chronic hepatitis C is liver histology; the rate of hepatic fibrosis may be slow, moderate, or rapid. Patients with mild necrosis and inflammation as well as those with limited fibrosis have an excellent prognosis and limited progression to cirrhosis. In contrast, among patients with moderate to severe necroinflammatory activity or fibrosis, including septal or bridging fibrosis, progression to cirrhosis is highly likely over the course of 10–20 years. The pace of fibrosis progression may be accelerated by such factors as concomitant HIV infection, other causes of liver disease, excessive alcohol use, and hepatic steatosis. Among patients with compensated cirrhosis associated with hepatitis C, the 10-year survival rate is close to 80%; mortality occurs at a rate of 2–6% per year; decompensation at a rate of 4–5% per year; and, as noted above, HCC at a rate of 1–4% per year. Estimates of the natural history of chronic hepatitis C have been made, based on data available on the prevalence of HCV infection in the U.S. population and on the rate of disease progression. Weighted primarily by the concentration of chronic hepatitis C in the baby boomer generation, the peak prevalence was estimated to have

occurred in 2015. The calculated frequency of cirrhosis in U.S. patients with hepatitis C was 5% in 1990, 25% in 2010, and is projected to be 37% in 2020. Estimated peak mortality has been predicted to occur in 2032. **A discussion of the pathogenesis of liver injury in patients with chronic hepatitis C appears in Chap. 332.**

Clinical features of chronic hepatitis C are similar to those described above for chronic hepatitis B. Generally, fatigue is the most common symptom; jaundice is rare. Immune complex–mediated extrahepatic complications of chronic hepatitis C are less common than in chronic hepatitis B (despite the fact that assays for immune complexes are often positive in patients with chronic hepatitis C), with the exception of essential mixed cryoglobulinemia **(Chap. 332)**, which is linked to cutaneous vasculitis and membranoproliferative glomerulonephritis as well as lymphoproliferative disorders such as B-cell lymphoma and unexplained monoclonal gammopathy. In addition, chronic hepatitis C has been associated with extrahepatic complications unrelated to immune-complex injury. These include Sjögren's syndrome, lichen planus, porphyria cutanea tarda, type 2 diabetes mellitus, and the metabolic syndrome (including insulin resistance and steatohepatitis).

Laboratory features of chronic hepatitis C are similar to those in patients with chronic hepatitis B, but aminotransferase levels tend to fluctuate more (the characteristic episodic pattern of aminotransferase activity) and to be lower, especially in patients with long-standing disease. An interesting and occasionally confusing finding in patients with chronic hepatitis C is the presence of autoantibodies. Rarely, patients with autoimmune hepatitis (see below) and hyperglobulinemia have false-positive immunoassays for anti-HCV. On the other hand, some patients with serologically confirmable chronic hepatitis C have circulating anti-LKM. These antibodies are anti-LKM1, as seen in patients with autoimmune hepatitis type 2 (see below), and are directed against a 33-amino-acid sequence of cytochrome P450 IID6. The occurrence of anti-LKM1 in some patients with chronic hepatitis C may result from the partial sequence homology between the epitope recognized by anti-LKM1 and two segments of the HCV polyprotein. In addition, the presence of this autoantibody in some patients with chronic hepatitis C suggests that autoimmunity may be playing a role in the pathogenesis of chronic hepatitis C.

Histopathologic features of chronic hepatitis C, especially those that distinguish hepatitis C from hepatitis B, are described in Chap. 332.

TREATMENT

Chronic Hepatitis C

Therapy for chronic hepatitis C has evolved substantially in the 25 years since IFN-α was introduced for this indication in 1991. The therapeutic armamentarium grew to include PEG IFN with ribavirin and, then, in 2011, the introduction of the first protease inhibitors, telaprevir and boceprevir, used in combination with PEG IFN and ribavirin in patients with HCV genotype 1. The field of antiviral therapy for hepatitis C was transformed beginning in 2013, with the approval of the first nucleoside analogue, sofosbuvir. As of 2016, no fewer than six, all-oral, highly effective (>95%), low-resistance, well tolerated, short-duration (usually 12 weeks) combination regimens of DAA drugs are available. The remarkable historical evolution of antiviral therapy for hepatitis C is instructive.

THE INTERFEON ERA (1991–2011)

IFN-based therapy has been supplanted by DAA agents introduced in the second decade of the twenty-first century; however, many important lessons about antiviral therapy for chronic hepatitis C were learned from the experience with IFN-based treatment, and many of the limitations of—and disparities in responsiveness to—IFN-based therapy have been overcome by current-generation DAA treatments. When first approved, IFN-α was administered via subcutaneous injection three times a week for 6 months but achieved an SVR **(Fig. 334-2)** (defined then as a reduction of HCV RNA to undetectable levels by PCR when measured ≥24 weeks after completion of therapy) <10%. Doubling the duration of therapy—but

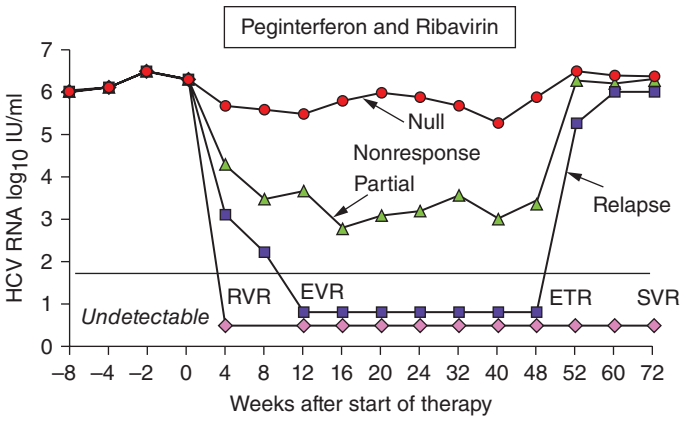

FIGURE 334-2 Classification of virologic responses based on outcomes during and after a 48-week course of pegylated interferon (PEG IFN) plus ribavirin antiviral therapy in patients with hepatitis C, genotype 1 or 4 (for genotype 2 or 3, the course would be 24 weeks). Nonresponders can be classified as null responders (hepatitis C virus [HCV] RNA reduction of <2 $\log_{10}$ IU/mL) or partial responders (HCV RNA reduction ≥2 $\log_{10}$ IU/mL but not suppressed to undetectable) by week 24 of therapy. In responders, HCV RNA can become undetectable, as shown with sensitive amplification assays, within 4 weeks (RVR, rapid virologic response); can be reduced by ≥2 $\log_{10}$ IU/mL within 12 weeks (early virologic response, EVR; if HCV RNA is undetectable at 12 weeks, the designation is "complete" EVR); or at the end of therapy, 48 weeks (ETR, end-treatment response). In responders, if HCV RNA remains undetectable for 24 weeks after ETR, week 72, the patient has a sustained virologic response (SVR), but if HCV RNA becomes detectable again, the patient is considered to have relapsed. The posttreatment week-24 SVR (SVR_{24}) has been supplanted by an SVR at week 12 (SVR_{12}), which has been shown to be equivalent to an SVR_{24}. In patients treated with DAA therapy, RVR and EVR milestones are largely irrelevant, being met by almost all patients. *(Reproduced with permission, courtesy of Marc G. Ghany, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health and the American Association for the Study of Liver Diseases. Hepatology 49:1335, 2009.)*

not increasing the dose or changing IFN preparations—increased the SVR rate to ~20%, and addition to the regimen of daily ribavirin, an oral guanosine nucleoside, increased the SVR rate to 40%. When used alone, ribavirin is ineffective and does not reduce HCV RNA levels appreciably, but ribavirin enhances the efficacy of IFN by reducing the likelihood of virologic relapse after the achievement of an end-treatment response (Fig. 334-2) (response measured during, and maintained to the end of, treatment). Proposed mechanisms to explain the role of ribavirin include subtle direct reduction of HCV replication, inhibition of host inosine monophosphate dehydrogenase activity (and associated depletion of guanosine pools), immune modulation, induction of virologic mutational catastrophe, and enhancement of IFN-stimulated gene expression. Ribavirin, despite its poorly understood mechanism of action, retains a modest role in supporting DAA agents as well (see below). IFN therapy results in activation of the JAK-STAT signal transduction pathway, which culminates in the intracellular elaboration of genes and their protein products that have antiviral properties. Hepatitis C proteins inhibit JAK-STAT signaling at several steps along the pathway, and exogenous IFN restores expression of IFN-stimulated genes and their antiviral effects.

Treatment with the combination of PEG IFN and ribavirin increased responsiveness (frequency of SVR) to as high as 55% overall—to >40% in genotypes 1 and 4, and to >80% in genotypes 2 and 3. Even in the absence of biochemical and virologic responses, histologic improvement occurred in approximately three-fourths of all treated patients. In chronic hepatitis C, ALT levels fall precipitously during therapy, and up to 90% of virologic responses are achieved within the first 12 weeks of therapy; responses thereafter are rare. Most relapses occur within the first 12 weeks after treatment; therefore, an SVR at week 12 posttreatment (SVR_{12}) is roughly equivalent to a 24-week SVR, and SVR_{12} has become the new standard. SVRs are very durable; normal ALT, improved histology, and absence of HCV RNA in serum and liver have been documented a decade after

successful therapy, and "relapses" 2 years after sustained responses are almost unheard of. Thus, an SVR to antiviral therapy of chronic hepatitis C is tantamount to a cure, which is followed by marked improvements in liver-disease outcomes (see below).

Patient variables that correlate with sustained virologic responsiveness to IFN-based therapy include favorable genotype (genotypes 2 and 3 as opposed to genotypes 1 and 4; genotype 1b as opposed to genotype 1a); low baseline HCV RNA level (<800,000 IU/mL), low HCV quasispecies diversity, and histologically mild hepatitis and minimal fibrosis, especially absence of cirrhosis; immunocompetence, low liver iron levels, age <40; female gender; and absence of obesity, insulin resistance, type 2 diabetes mellitus, and hepatic steatosis. High levels of HCV RNA, more histologically advanced liver disease, and high HCV quasispecies diversity all go hand in hand with advanced duration of infection and reduced IFN responsiveness. Also associated with poor responses to IFN-based therapy are African-American ethnicity (contributed to, but not explained entirely by, a higher proportion with genotype 1, slower early treatment viral kinetics, impaired HCV-specific immunity, and host genetic differences in *IL28B* alleles, described below), Latino ethnicity, and poor treatment adherence (<80% of IFN and ribavirin doses and <80% of prescribed duration of therapy). Ironically, patients whose disease was least likely to progress were the ones *most* likely to respond to IFN and vice versa. For patients treated with combination IFN-ribavirin, therapy for those with genotype 1 usually required a full 48 weeks with SVRs in the range of 40–45%, whereas in those with genotypes 2 and 3, a 24-week course of therapy sufficed with SVRs in the range of 80% (although refined tailoring of treatment duration could be indicated based on rapidity of response or associated cofactors, see below).

Genetic changes in the virus may explain differences in treatment responsiveness in some patients (e.g., among patients with genotype 1b, responsiveness to IFN is enhanced in those with amino-acid-substitution mutations in the nonstructural protein 5A gene). As described above in the discussion of spontaneous recovery from acute hepatitis C, IFN gene variants discovered in genome-wide association studies were shown to have a substantial impact on responsiveness of patients with genotype 1 to antiviral therapy. In studies of patients treated with PEG IFN and ribavirin, variants of the *IL28B* SNP that code for IFN-λ3 (a type III IFN, the receptors for which are more discretely distributed than IFN-α receptors and more concentrated in hepatocytes) correlate significantly with responsiveness. Patients homozygous for the C allele at this locus have the highest frequency of achieving an SVR (~80%), those homozygous for the T allele at this locus are least likely to achieve an SVR (~25%), and those heterozygous at this locus (C/T) have an intermediate level of responsiveness (SVRs in ~35%).

Side effects of IFN therapy are described in the section on treatment of chronic hepatitis B. The most pronounced side effect of ribavirin therapy is hemolysis—an expected reduction in hemoglobin of up to 2–3 g or in hematocrit of 5–10% but also a small, unpredictable proportion with profound, brisk hemolysis, resulting in symptomatic anemia; therefore, close monitoring of blood counts is crucial, and ribavirin should be avoided in patients with anemia or hemoglobinopathies; in patients with coronary artery disease or cerebrovascular disease, in whom anemia can precipitate an ischemic event; in patients with renal insufficiency (the drug is excreted renally); and in pregnancy (the drug is teratogenic, mandating scrupulous use of efficient contraception during, and for several months after, therapy in women of child-bearing age [because of their antiproliferative properties, IFNs also are contraindicated during pregnancy]). When symptomatic anemia occurs, ribavirin dose reductions or addition of erythropoietin to boost red blood cell levels may be required; erythropoietin was shown to improve patients' quality of life but not the likelihood of achieving an SVR. If ribavirin was stopped during therapy, SVR rates fell, but responsiveness could be maintained as long as ribavirin was not stopped and the total ribavirin dose exceeded 60% of the planned dose.

Ribavirin can also cause nasal and chest congestion, pruritus, and precipitation of gout. Combination IFN-ribavirin therapy is more difficult to tolerate than IFN monotherapy and more likely to lead to dose reductions and discontinuation of therapy.

Studies of viral kinetics have shown that despite a virion half-life in serum of only 2–3 h, the level of HCV is maintained by a high replication rate of 10^{12} hepatitis C virions per day. IFN-α blocks virion production or release with an efficacy that increases with increasing drug doses; moreover, the calculated death rate for infected cells during IFN therapy is inversely related to the level of HCV RNA. Patients with the most rapid death rate of infected hepatocytes are more likely to achieve undetectable HCV RNA at 3 months; in practice, failure to achieve an early virologic response (EVR), a ≥2-$\log_{10}$ reduction in HCV RNA by week 12, predicts failure to experience a subsequent SVR. Similarly, patients in whom HCV RNA becomes undetectable within 4 weeks (i.e., who achieve a rapid virologic response [RVR]) have a very high likelihood of achieving an SVR (Fig. 334-2). Surprisingly, however, high-dose induction with IFN-based therapy did not yield higher SVR rates.

For the treatment of chronic hepatitis C, standard IFNs were supplanted beginning in 2001 by PEG IFNs. These have elimination times up to sevenfold longer than standard IFNs (i.e., a substantially longer half-life) and achieve prolonged concentrations, permitting administration once (rather than three times) a week. Instead of the frequent drug peaks (linked to side effects) and troughs (when drug is absent) associated with frequent administration of short-acting IFNs, administration of PEG IFNs results in drug concentrations that are more stable and sustained over time. Once-a-week PEG IFN monotherapy is twice as effective as monotherapy with its standard IFN counterpart, approaches the efficacy of combination standard IFN plus ribavirin, and is as well tolerated as standard IFNs, without more difficult-to-manage thrombocytopenia and leukopenia than standard IFNs. For most of the decade prior to 2011, when protease inhibitors were introduced for HCV genotype 1 (see below), the standard of care was a combination of PEG IFN plus ribavirin for all HCV genotypes.

Two PEG IFNs are available: PEG IFN-α2b, a 12-kD, linear PEG molecule bound to IFN-α2b, and PEG IFN-α2a, a larger, 40-kD, branched PEG molecule bound to IFN-α2a; because of its larger size and smaller volume of extravascular distribution, PEG IFN-α2a can be given at a uniform dose independent of weight, whereas the dose of the smaller PEG IFN-α2b, which has a much wider volume distribution, must be weight-based. The standard dose of PEG IFN α2a was 180 μg and of PEG IFN-α2b 1.5 μg/kg. The ribavirin dose adopted for both PEG IFNs was, for genotype 1, 1000 mg (for patients <75 kg) to 1200 mg (for patients ≥75 kg) and, for genotypes 2 and 3, 800 mg; a broader ribavirin dose/weight range was approved subsequently for PEG IFN-α2b in patients with genotype 1: <65 kg, 800 mg; 65–85 kg, 1000 mg; >85–105 kg, 1200 mg; and >105 kg, 1400 mg. For both drugs, recommended treatment durations were 48 weeks for genotype 1 and 24 weeks for genotypes 2 and 3 (somewhat more refractory, justifying a full 48 weeks especially for advanced hepatic fibrosis or cirrhosis and/or high-level HCV RNA). Between the two PEG IFNs, PEG IFN-α2a appeared to be slightly better tolerated and slightly more effective than PEG IFN-α2b in registration trials (SVRs for genotype 1: 41–51% vs 40–42%, respectively) as well as in subsequent head-to-head trials and a systematic review of randomized trials (SVR in genotypes 1–4: 48–55% vs 32–40%, respectively).

Until the 2011 introduction of protease inhibitors, unless ribavirin was contraindicated (see above), combination PEG IFN plus ribavirin was the recommended course of therapy. Even after the introduction of protease inhibitors for genotypes 1 and 4, however, PEG IFN–ribavirin remained the standard of care for patients with genotypes 2 and 3 until late 2013. For patients treated with combination PEG IFN–ribavirin, measurement of quantitative HCV RNA levels at 12 weeks was helpful in guiding therapy; if a 2-$\log_{10}$ drop in HCV RNA had not been achieved by this time, chances for an SVR were negligible, and additional therapy was futile. If the 12-week HCV RNA had fallen by 2 $\log_{10}$ (EVR), the chances for an SVR at the end of therapy were approximately two-thirds; if the 12-week HCV

RNA was undetectable ("complete" EVR), the chances for an SVR exceeded 80% (Fig. 334-2).

The frequency of an SVR to PEG IFN–ribavirin therapy could be increased by tailoring therapy according to baseline variables and on-treatment virologic responsiveness. In patients with baseline variables weighing against a response (e.g., HCV RNA >800,000 IU/mL, weight >85 kg), by raising the dose of PEG IFN (e.g., to as high as 270 μg of PEG IFN-α2a) and/or the dose of ribavirin to as high as 1600 mg daily (if tolerated or supplemented by erythropoietin); or by extending therapy from 48 to 72 weeks for patients with genotype 1 and a slow virologic response (i.e., failure of HCV RNA to fall rapidly to undetectable levels within 4 weeks [absence of a RVR]), SVR rates could be improved somewhat. In contradistinction, in patients with genotype 1 (and 4) who had a 4-week RVR (which occurred in ≤20%), especially in the subset with low baseline HCV RNA, abbreviating the duration of therapy to 24 weeks, resulted in SVR rates of ~90%. Responsiveness to IFN-ribavirin-based therapy was diminished in immunocompromised patients and in patients with HIV-HCV co-infection and contraindicated in patients with decompensated liver disease or end-stage renal disease. The cumbersome nature of IFN-ribavirin-based therapy (injections, complicated laboratory monitoring, side effects and poor tolerability, modest efficacy, variables and patient subsets associated with poor responsiveness, tailored therapy, futility rules, etc.) was supplanted eventually (in 2016) by DAAs for all genotypes (see below). Most of the variables associated with poor responsiveness to IFN-based therapy became irrelevant, and difficult-to-treat patient subpopulations began to experience responses to DAAs that were indistinguishable from responses in standard patients (see below).

Persons with chronic HCV infection have been shown to suffer increased liver-related mortality. On the other hand, successful antiviral therapy of chronic hepatitis C resulting in an SVR has been shown to improve survival (and to reduce the need for liver transplantation); to lower the risk of liver failure, liver-related death, and all-cause mortality; to slow the progression of chronic hepatitis C; and to reverse fibrosis and even cirrhosis. Whereas the 10-year and 20-year survival in the absence of an SVR is reduced in cirrhotic patients with chronic hepatitis C, survival at these intervals after an SVR has been found to be indistinguishable from that of the general population. Although successful treatment reduces mortality and liver failure (3-4-fold 10-year reduction) in cirrhotic patients (and in those with advanced fibrosis) and reduces the need for liver transplantation and the likelihood of HCC (14-fold 10-year reduction), the risk of liver-related death and HCC persists, albeit at a much reduced level, necessitating continued clinical monitoring and cancer surveillance after SVR in cirrhotics. On the other hand, in the absence of an SVR, IFN-based therapy does not reduce the risk of HCC. Similarly, for nonresponders to PEG IFN–ribavirin therapy, three trials of long-term maintenance therapy with PEG IFN showed no benefit in reducing the risk of histologic progression or clinical decompensation, including the development of HCC. Fortunately, PEG IFN-ribavirin nonresponders can now be retreated with DAAs and experience SVR rates comparable to those in treatment-naïve persons (see below).

FIRST-GENERATION PROTEASE INHIBITORS (2011–2013)

The HCV RNA genome encodes a single polyprotein, which is cleaved during and after translation by host and viral-encoded proteases. One protease involved in the cleavage of the viral polyprotein is an NS3/4A viral protein that has serine protease activity. Telaprevir and boceprevir are serine protease inhibitors that target NS3/4A. In 2011, telaprevir and boceprevir used in combination with PEG IFN and ribavirin were approved by the U.S. Food and Drug Administration (FDA) as the first oral DAA agents for the treatment of hepatitis C genotype 1 (not other genotypes) in adults with stable liver disease, both in patients who had not been treated before or who had failed previous treatment. Although now replaced by more effective, all-oral regimens, these first-in-class agents represented a breakthrough in the treatment of chronic hepatitis C and established milestones against which subsequent therapies could be measured.

Because resistance developed rapidly during monotherapy with telaprevir and boceprevir, these drugs had to be used in combination with PEG IFN and ribavirin. Ribavirin in particular appeared to reduce relapse rates significantly in protease inhibitor-based regimens, such that those who could not take or were intolerant to ribavirin were unlikely to benefit from the addition of these agents. Telaprevir and boceprevir regimens consisted of periods of triple therapy (protease inhibitor plus PEG IFN plus ribavirin) and periods of dual therapy (PEG IFN plus ribavirin). Telaprevir regimens began with 12 weeks of triple therapy followed by dual therapy of a duration based on HCV RNA status at weeks 4 and 12 ("response-guided therapy") and prior treatment status. Boceprevir-based regimens consisted of a 4-week lead-in period of dual (PEG IFN–ribavirin) therapy followed by triple therapy and, in some instances, a further extension of dual therapy, with duration of response-guided therapy based on HCV RNA status at weeks 4, 8, and 24 and prior treatment status.

For patients with HCV genotype 1, protease inhibitors improved the frequency of RVRs and SVRs significantly as compared to PEG IFN plus ribavirin alone. In treatment-naïve patients, telaprevir-based SVRs were achieved in up to 79% of patients who received 12 weeks of triple therapy followed by 12–36 weeks of dual therapy, and among those with EVRs (undetectable HCV RNA at weeks 4 and 12) and response-guided therapy stopped at week 24 (12 weeks of triple therapy, then 12 weeks of dual therapy), SVRs occurred in 83–92%. In studies with boceprevir in treatment-naïve patients, SVRs occurred in 59–66% of patients, and among those with undetectable HCV RNA at 8 weeks, the SVR rate increased to 86–88%. Adding to the complexity of treatment with these protease inhibitors were absolute stopping rules for futility, that is, absence of HCV RNA reductions at critical treatment milestones, which were shown to be invariably predictive of nonresponse (telaprevir: HCV RNA >1000 IU/mL at weeks 4 or 12, or detectable at week 24; boceprevir: HCV RNA ≥100 IU/mL at week 12, or detectable at week 24).

In patients previously treated unsuccessfully with PEG IFN plus ribavirin, telaprevir-based treatment achieved SVRs in 83–88% of prior relapsers, 54–59% of partial responders (HCV RNA reduced by ≥2 $\log_{10}$ IU/mL but not to undetectable levels), and 29–33% of null responders (HCV RNA reduced by <2 $\log_{10}$ IU/mL). With boceprevir, a similar degradation in SVR rate occurred as a function of prior responsiveness—in 75% of prior relapsers, in 40–52% of previous partial responders; in ~30–40% of null responders. In a substantial proportion of protease inhibitor nonresponders, resistance-associated substitutions (RASs, previously referred to as resistance-associated variants, RAVs) could be identified, but these variants were not archived, and wild-type HCV reemerged in almost all cases within 1.5 to 2 years. SVRs to these protease inhibitors were highest in prior relapsers and treatment-naïve patients (white > black ethnicity), lower in prior partial responders, lower still in prior null responders, and lowest in cirrhotic prior null responders, for whom no benefit accrued over PEG IFN/ribavirin treatment. Responses to protease inhibitor triple-drug regimens were higher in patients with *IL28B* C than non-C genotypes, HCV genotype 1b than genotype 1a, less advanced than more advanced fibrosis stage, whites than blacks, lower body mass index (BMI) than elevated BMI, and, for boceprevir, achievement of a >1 $\log_{10}$ HCV RNA reduction during 4 weeks of PEG IFN–ribavirin lead-in therapy. Age and HCV RNA level were less influential and insulin resistance was noninfluential on response to these antiviral agents.

Both of these protease inhibitors had substantial toxicities. Telaprevir was associated with a severe, generalized (trunk and extremities), often confluent, maculopapular, pruritic rash in ~6% of treated patients (that required careful dermatologic monitoring in all patients and systemic corticosteroid therapy in the most severely affected). Other common side effects included pruritus, rectal burning, nausea, diarrhea, fatigue, dysgeusia (altered or unpleasant taste), and anemia, which required close monitoring, could be relatively refractory, occasionally requiring transfusion and even hospitalization (especially in cirrhotic prior nonresponders). Anemia occurred in half of boceprevir-treated patients, neutropenia in up to 30% and thrombocytopenia

in 3–4%. Other side effects of boceprevir include fatigue, nausea, headache, dysgeusia, dry mouth, vomiting, and diarrhea.

Both drugs came with an inconveniently high pill burden and had to be administered every 8 hours with food (TVR with a 20-g fat meal). Use of protease inhibitors was further complicated by numerous drug-drug interactions. As telaprevir and boceprevir are both eliminated by and inhibit CYP3A4, these agents could not be administered with other medications that induce CYP3A4 or are dependent on CYP3A4 for elimination. Care had to be taken to examine for any potential interactions between these protease inhibitors and other medications the patient was taking, and a convenient website became available to check for such drug-drug interactions (*www.hep-druginteractions.org*).

Despite the improvement in SVRs with protease-inhibitor-based regimens for genotype 1 compared to PEG IFN-ribavirin (e.g., in treatment-naïve patients 66–79% vs 38–44%), triple-drug protease-inhibitor therapy was hampered by amplified intolerability, the complexity of response-guided regimens and futility stopping rules, the inconvenience of thrice-daily dosing with meals and a high pill burden, the need for PEG IFN injections and ribavirin with all their intolerability, and multiple drug-drug interactions. Moreover, side effects appeared to be more severe and burdensome once these drugs entered practice, especially in cirrhotic nonresponders, in whom studies reported from Europe showed serious adverse events in up to 45% and deaths in up to 3%. All these issues, as well as rapidly accelerating progress on next-generation and all-oral DAA therapy (see below), conspired to temper enthusiasm for these new antivirals; after a brief stint as recommended therapy (2011–2013), these drugs became obsolete and are no longer recommended.

CONTEMPORARY DIRECT-ACTING ANTIVIRAL COMBINATION THERAPY (2013–)

Since late 2013, the number of new antiviral agents for hepatitis C has expanded substantially, and, currently, PEG IFN-based treatments have been supplanted by six therapeutic regimens: all oral, IFN-free, highly efficacious (>95% SVR), well tolerated, with high barriers to resistance, simple dosing and low pill burdens, treatment durations as brief as 8 to 12 weeks, and, in many cases, pangenotypic efficacy (**Table 334-6**). These drugs are distributed among three classes of DAAs: NS3/4 protease inhibitors (which cleave the single HCV polyprotein into constituent structural and nonstructural proteins), NS5B nucleoside and nonnucleoside polymerase inhibitors (which interfere with the RNA-dependent RNA polymerase [a replicase] involved in synthesis of viral RNA), and NS5A inhibitors (which interfere with a membrane-associated phosphoprotein essential to the HVC RNA replication complex).

The first of the new DAA agents (approved in November 2013) was simeprevir, a second-generation protease inhibitor for genotype 1, followed shortly thereafter (December 2013) by sofosbuvir, a pangenotypic nucleoside polymerase inhibitor. For genotype 1, both of these agents had to be combined with PEG IFN and ribavirin; for genotypes 2 and 3, sofosbuvir was administered with ribavirin, without PEG IFN; however, these treatment regimens have been supplanted by combinations of all-oral, IFN-free, DAAs, and ribavirin is rarely needed, retained only for very limited indications.

Simeprevir: When simeprevir was used with PEG IFN, its efficacy (genotype 1b > 1a) was similar to that of first-generation protease inhibitors, but required only once-a-day dosing without the complexity of response-guided therapy. Similar to first-generation protease inhibitors, simeprevir was hampered by many drug-drug interactions and side effects (including photosensitivity, rash, and mild hyperbilirubinemia); moreover, patients, with HCV NS3 polymorphism Q80K had markedly reduced drug efficacy, necessitating pretreatment genetic testing and disqualifying a substantial proportion (approximately a third) of potential treatment candidates. Little about simeprevir supported its adoption in combination with PEG IFN and ribavirin. On the other hand, the combination of simeprevir (150 mg) along with sofosbuvir (400 mg) for 12 weeks was found to be effective in treatment-naïve (97% SVR_{12}) or treatment-experienced (95% SVR_{12}) patients without cirrhosis and in treatment-naïve (88% SVR_{12}) or treatment-refractory (79% SVR_{12}) patients with cirrhosis (it remains one of the recommended regimens for genotype 1).

Sofosbuvir: Sofosbuvir, the first nonprotease inhibitor DAA to be approved, has an excellent profile—high potency, high barrier to resistance, pangenotypic activity, very well tolerated with limited adverse effects (most commonly mild fatigue, insomnia, headache, and nausea), once-daily oral administration, and relative freedom from major drug-drug interactions. Sofosbuvir has efficacy in all genotypes (1 to 6); in treatment-naïve subjects and prior nonresponders to PEG IFN-based and protease-inhibitor-based therapy; with PEG IFN-RBV or in IFN-free regimens; in combination with RBV or with NS5A inhibitors; and for treatment periods as brief as 8 to 12 weeks to as long as 24 weeks. Currently, sofosbuvir is used in combination with either the protease inhibitor simeprevir (as described above) or, more commonly, with one of three NS5A inhibitors. Thus, sofosbuvir is a component of four of the six recommended DAA regimens for genotype 1, two of the four regimens for genotype 4, and both of the regimens for genotypes 2, 3, 5, and 6 (Table 334-6).

Sofosbuvir/ledipasvir: The DAA combination that has had a dominant role in the treatment of hepatitis C is sofosbuvir (400 mg) plus the NS5A inhibitor ledipasvir (90 mg) in a once-a-day, fixed-dose, single pill, approved in October 2014 for genotype 1 and in November 2015 for genotypes 4, 5, and 6. Phase-III trials were conducted in treatment-naïve noncirrhotic patients, in treatment-naïve cirrhotic and noncirrhotic patients, and in treatment-experienced cirrhotic and noncirrhotic patients treated for 8, 12, or 24 weeks, both with and without ribavirin. In treatment-naïve noncirrhotics, an SVR_{12} was achieved in 97–99% of subjects, and no benefit was observed by extending therapy from 12 to 24 weeks or by adding ribavirin. Moreover, for treatment-naïve, noncirrhotic patients with baseline HCV RNA $<6 \times 10^6$ IU/mL, a treatment duration of 8 weeks was as effective as one of 12 weeks (94–95% SVR_{12}), which may be a consideration for a proportion of patients. In cirrhotic patients, SVR_{12} was achieved in 97–100% of treatment-naïve subjects (no advantage of extending therapy from 12 to 24 weeks or of adding ribavirin); however, for cirrhotic prior nonresponders to IFN-based therapy, 12 weeks of therapy was inferior (86% SVR_{12}) to 24 weeks of therapy (100% SVR_{12}). This combination, which is equally effective in patients with HIV-HCV co-infection and in African-American patients, has been shown to be highly effective in patients with decompensated cirrhosis and in patients with hepatitis C after liver transplantation and after kidney transplantation. On the other hand, the safety and efficacy of sofosbuvir/ledipasvir in patients with advanced renal failure have not been established, and all sofosbuvir-containing regimens can be associated with severe bradycardia in patients taking the antiarrhythmic agent amiodarone, especially along with beta blockers; sofosbuvir-containing combinations are contraindicated with amiodarone. Drug-drug interactions are few, but P-gp inducers, like St. John's wort and rifampin, and proton-pump gastric acid inhibitors, like omeprazole, may reduce sofosbuvir/ledipasvir concentrations. Generally, responsiveness to sofosbuvir/ledipasvir is not reduced in patients with baseline RASs to these agents, with the exception of treatment-experienced patients who have baseline NS5A RASs (for whom EASL recommends adding ribavirin or, if ribavirin in contraindicated, extending treatment to 24 weeks).

Paritaprevir/ritonavir, ombitasvir, and dasabuvir: The combination of ritonavir (100 mg)-boosted paritaprevir (150 mg), a protease inhibitor; ombitasvir (25 mg), an NS5A inhibitor; dasabuvir (250 mg), a nonnucleoside polymerase inhibitor; ± weight-based ribavirin (total of five drugs) was approved in December 2014 for genotypes 1 and 4. Paritaprevir/ritonavir and ombitasvir, formulated in a single tablet, are taken once daily, and both dasabuvir (a separate pill) and weight-based ribavirin (when included in the regimen) are taken twice daily. In clinical trials, this combination achieved SVR_{12} rates of 87–100% in treatment-naïve and treatment-experienced patients with genotype 1; without ribavirin, this combination in

TABLE 334-6 Indications and Recommendations for Antiviral Therapy of Chronic Hepatitis C[a]

Standard Indications for Therapy

All patients with chronic HCV infection (detectable HCV RNA, with or without elevated ALT) except for those with short life expectancies owing to comorbid conditions.

Any stage of fibrosis; highest priority for advanced fibrosis [METAVIR stage 3]/cirrhosis [METAVIR stage 4] (pretreatment biopsy is no longer embraced and has been supplanted by noninvasive measures of fibrosis, e.g., imaging to determine liver elasticity)

Responsiveness in groups previously refractory to interferon-based therapy (HIV-HCV co-infection, renal insufficiency, African American and Latino ethnicity, *IL28B* non-C haplotype, obesity, insulin resistance, hepatic decompensation, etc.) is not diminished to contemporary direct-acting oral combination regimens.

Retreatment Recommended

Relapsers, partial responders, or nonresponders after a previous course of interferon-based therapy or prior direct-acting antiviral therapy (see genotype-specific recommendations below).

Antiviral Therapy Not Recommended

Pregnancy: No clinical studies of direct-acting antivirals during pregnancy are available. Ribavirin is contraindicated during pregnancy; therefore, any regimen including ribavirin should not be used. Sofosbuvir; sofosbuvir + ledipasvir; and paritaprevir/ritonavir + ombitasvir + dasabuvir are classified as pregnancy category B, but the other direct-acting antivirals do not have a pregnancy classification. Therefore, these therapies are not indicated routinely in pregnancy and should be used, with caution, only if the benefit of treatment outweighs the potential for fetal risk.

Therapeutic Regimens (based on AASLD-IDSA recommendations, *www.hcvguidelines.org*)[b]

The European Association for the Study of the Liver (EASL) issued recommendations in 2016; divergences from AASLD-IDSA recommendations are summarized as a footnote below.[c]

TREATMENT-NAÏVE OR RELAPSED AFTER PRIOR PEG IFN/RIBAVIRIN THERAPY

Genotype 1a

ledipasvir + sofosbuvir 12 weeks (consider 8 weeks for noncirrhotic patients with HCV RNA <6 × 10^6 IU/mL)

paritaprevir/ritonavir + ombitasvir + dasabuvir + RBV 12 weeks (no cirrhosis) or 24 weeks (cirrhosis)

sofosbuvir + simeprevir 12 weeks (no cirrhosis) or ± RBV 24 weeks (cirrhosis)

daclatasvir + sofosbuvir 12 weeks (no cirrhosis) or ± RBV 24 weeks (cirrhosis)

grazoprevir + elbasvir 12 weeks (no cirrhosis or cirrhosis sans ELB NS5A RASs) or + RBV × 16 weeks (ELB NS5A RASs)

sofosbuvir + velpatasvir 12 weeks

Genotype 1b

ledipasvir + sofosbuvir 12 weeks (consider 8 weeks for noncirrhotic patients with HCV RNA <6 × 10^6 IU/mL)

paritaprevir/ritonavir + ombitasvir + dasabuvir 12 weeks

sofosbuvir + simeprevir 12 weeks (no cirrhosis) or ± RBV 24 weeks (cirrhosis)

daclatasvir + sofosbuvir 12 weeks (no cirrhosis) or ± RBV 24 weeks (cirrhosis)

grazoprevir + elbasvir 12 weeks

sofosbuvir + velpatasvir 12 weeks

Genotype 2

sofosbuvir + velpatasvir 12 weeks

daclatasvir + sofosbuvir (no cirrhosis) 12 weeks or 16–24 weeks (cirrhosis)

Genotype 3

sofosbuvir + velpatasvir 12 weeks

daclatasvir + sofosbuvir 12 weeks (no cirrhosis) or ± RBV 24 weeks (cirrhosis)

Genotype 4

sofosbuvir + velpatasvir 12 weeks

ledipasvir + sofosbuvir 12 weeks

paritaprevir/r + ombitasvir + RBV 12 weeks (no dasabuvir)

grazoprevir + elbasvir 12 weeks

Genotypes 5, 6

sofosbuvir + velpatasvir 12 weeks

ledipasvir + sofosbuvir 12 weeks

FAILED PRIOR PEG IFN/RIBAVIRIN THERAPY, NO CIRRHOSIS

Genotype 1a

ledipasvir + sofosbuvir 12 weeks

paritaprevir/ritonavir + ombitasvir + dasabuvir + RBV 12 weeks

sofosbuvir + simeprevir 12 weeks

daclatasvir + sofosbuvir 12 weeks

grazoprevir + elbasvir 12 weeks (without ELB NS5A RASs) or + RBV x 16 weeks (ELB NS5A RASs)

sofosbuvir + velpatasvir 12 weeks

Genotype 1b

ledipasvir + sofosbuvir 12 weeks

paritaprevir/ritonavir + ombitasvir + dasabuvir 12 weeks

sofosbuvir + simeprevir 12 weeks

daclatasvir + sofosbuvir 12 weeks

grazoprevir + elbasvir 12 weeks

sofosbuvir + velpatasvir 12 weeks

Genotype 2

sofosbuvir + velpatasvir 12 weeks

daclatasvir + sofosbuvir 12 weeks

Genotype 3

sofosbuvir + velpatasvir 12 weeks

daclatasvir + sofosbuvir 12 weeks

Genotype 4

sofosbuvir + velpatasvir 12 weeks

ledipasvir + sofosbuvir 12 weeks

paritaprevir/r + ombitasvir + RBV 12 weeks (no dasabuvir)

grazoprevir + elbasvir 12 weeks (prior relapse) or + RBV 16 weeks (prior nonresponse)

Genotypes 5, 6

sofosbuvir + velpatasvir 12 weeks

ledipasvir + sofosbuvir 12 weeks

FAILED PRIOR PEG IFN/RIBAVIRIN THERAPY, COMPENSATED CIRRHOSIS

Genotype 1a

ledipasvir + sofosbuvir + RBV 12 weeks

ledipasvir + sofosbuvir 24 weeks

sofosbuvir + velpatasvir 12 weeks

grazoprevir + elbasvir 12 weeks (without ELB NS5A RASs) or + RBV × 16 weeks (ELB NS5A RASs)

paritaprevir/ritonavir + ombitasvir + dasabuvir + RBV 24 weeks

sofosbuvir + simeprevir ± RBV 24 weeks (no Q80K variant)

daclatasvir + sofosbuvir ± RBV 24 weeks

Genotype 1b

ledipasvir + sofosbuvir + RBV 12 weeks

ledipasvir + sofosbuvir 24 weeks

sofosbuvir + velpatasvir 12 weeks

grazoprevir + elbasvir 12 weeks

paritaprevir/ritonavir + ombitasvir + dasabuvir 12 weeks

sofosbuvir + simeprevir ± RBV 24 weeks

daclatasvir + sofosbuvir ± RBV 24 weeks

Genotype 2

sofosbuvir + velpatasvir 12 weeks

sofosbuvir + daclatasvir 16 or 24 weeks

Genotype 3

sofosbuvir + velpatasvir 12 weeks

daclatasvir + sofosbuvir + RBV 24 weeks

Genotype 4

sofosbuvir + velpatasvir 12 weeks

ledipasvir + sofosbuvir + RBV 12 weeks

(*Continued*)

TABLE 334-6 Indications and Recommendations for Antiviral Therapy of Chronic Hepatitis C[a] (Continued)

paritaprevir/ritonavir + ombitasvir + RBV 12 weeks (no dasabuvir)	**FEATURES ASSOCIATED WITH REDUCED RESPONSIVENESS TO DIRECT-ACTING ANTIVIRAL COMBINATION THERAPY**
grazoprevir + elbasvir 12 weeks (prior relapse) or + RBV 16 weeks (prior nonresponse)	Genotype and subtype (genotype 1a less responsive than genotype 1b for several drugs)
ledipasvir + sofosbuvir 24 weeks	Treatment experience
Genotypes 5, 6	Advanced fibrosis (bridging fibrosis, cirrhosis)
sofosbuvir + velpatasvir 12 weeks	Reduced adherence
ledipasvir + sofosbuvir 12 weeks	

[a]Rapidly evolving new recommendations continue to be issued; for up-to-date treatment recommendations, please see *www.hcvguidelines.org*. [b]Class-I recommendations in **bold** font, all others are Class-II recommendations [c]The following EASL recommendations differ from those of AASLD-IDSA (Please note that, although mentioned in EASL recommendations, testing for baseline RASs is not recommended routinely, but, if reliable resistance testing available, results can be used to guide therapy.):

Genotype 1

For genotype 1, simeprevir + sofosbuvir is not recommended.

For genotype 1a, treatment-experienced patients (IFN-based regimen failures) treated with sofosbuvir + ledipasvir should have weight-based ribavirin added. If reliable testing for RASs is available, ribavirin is needed only if baseline RASs are present, and, in such patients, if ribavirin is contraindicated, sofosbuvir + ledipasvir should be extended to 24 weeks.

For genotype 1b, in treatment-naïve, noncirrhotic patients receiving paritaprevir/ritonavir + ombitasvir + dasabuvir a treatment duration of 8 weeks can be considered.

For genotype 1a, in patients treatment with grazoprevir + elbasvir, EASL recommends testing for ELB RASs even in noncirrhotics. If resistance testing is not done, the level of baseline HCV RNA should determine whether ribavirin is added and the duration of therapy. If HCV RNA >800,000 IU/mL, add ribavirin and treat for 16 weeks; if HCV RNA ≤800,000 IU/mL, ribavirin is not added, and treatment for 12 weeks suffices. If baseline testing for RASs is available, patients with HCV RNA >800,000 IU/mL and detectable RASs should be treated with ribavirin for 16 weeks. Treatment without ribavirin and for 12 weeks suffices if HCV RNA ≤800,000 IU/mL even with detectable RASs or even if HCV RNA >800,000 IU/mL with undetectable RASs.

For genotype 1a, in treatment-experienced patients (IFN-based regimen failures) treated with daclatasvir + sofosbuvir, follow the same recommendations described above for ledipasvir + sofosbuvir regarding the addition of ribavirin.

Genotype 2

EASL recommendations are the same as those of AASLD-IDSA.

Genotype 3

For treatment-experienced patients (IFN-based regimen failures) treated with sofosbuvir + velpatasvir or sofosbuvir + daclatasvir, if testing for baseline RASs is not available, add weight-based ribavirin. If resistance testing is available, ribavirin is needed only if baseline RASs are present, and, in such patients, if ribavirin is contraindicated, treatment should be extended to 24 weeks.

Genotype 4

Treatment-experienced patients (IFN-based regimen failures) treated with sofosbuvir + ledipasvir should have weight-based ribavirin added, and, in such patients, if ribavirin is contraindicated, treatment should be extended to 24 weeks.

In treatment-experienced patients (IFN-based regimen failures) treated with grazoprevir + elbasvir, if HCV RNA >800,000 IU/mL, weight-based ribavirin should be added, and treatment should be extended to 16 weeks.

EASL recommends two additional treatment options for genotype 4 (noncirrhotic or cirrhotic) that are not included in AASLD-IDSA guidelines: sofosbuvir + daclatasvir and sofosbuvir + simeprevir. For both these options, treatment-naïve patients should be treated for 12 weeks without ribavirin; treatment-experienced (IFN-based regimen failures) patients should be treated with ribavirin for 12 weeks or, if ribavirin is contraindicated, without ribavirin for 24 weeks.

Genotypes 5 and 6

Treatment-experienced patients (IFN-based regimen failures) treated with sofosbuvir + ledipasvir should have weight-based ribavirin added, and, in such patients, if ribavirin is contraindicated, treatment should be extended to 24 weeks.

EASL recommends an additional treatment option for genotype 5 and 6 (noncirrhotic or cirrhotic) that is not included in AASLD-IDSA guidelines: sofosbuvir + daclatasvir. Treatment-naïve patients should be treated for 12 weeks without ribavirin; treatment-experienced (IFN-based regimen failures) patients should be treated with ribavirin for 12 weeks or, if ribavirin is contraindicated, without ribavirin for 24 weeks.

Drug doses: sofosbuvir 400 mg; ledipasvir 90 mg; paritaprevir 150 mg; ritonavir 100 mg; ombitasvir 25 mg; dasabuvir 250 mg; ribavirin, weight-based: 1000 mg (<75 Kg)–1200 mg (≥75 kg); simeprevir 150 mg; daclatasvir 60 mg; elbasvir 50 mg; grazoprevir 100 mg; velpatasvir 100 mg.

Abbreviations: AASLD, American Association for the Study of Liver Diseases; ALT, alanine aminotransferase; ELB NS5A RASs, elbasvir NS5A resistance-associated substitutions; HCV, hepatitis C virus; IFN, interferon; IDSA, Infectious Diseases Society of America; PEG IFN, pegylated interferon; IU, international units (1 IU/mL is equivalent to ~2.5 copies/mL); RASs, resistance-associated substitutions; RBV, ribavirin.

genotype 1a is ~7% less responsive than genotype 1b. Therefore, in treatment-naïve patients with genotype 1a, this combination is administered *with* ribavirin for 12 weeks in the absence of cirrhosis (95–97% SVR_{12}) or for 24 weeks in the presence of compensated cirrhosis (94% SVR_{12}), while in patients with genotype 1b, the combination does not require ribavirin, and the duration of therapy is 12 weeks for both noncirrhotics and cirrhotics (99–100% SVR_{12}). In prior nonresponders without cirrhosis, the combination is administered for 12 weeks, *with* ribavirin in genotype 1a (96% SVR_{12}), *without* ribavirin in genotype 1b (100% SVR_{12}). In prior nonresponders with cirrhosis, the combination is administered for 24 weeks *with* ribavirin in genotype 1a (SVR_{12} 100% in prior relapsers and partial responders, 95% in prior null responders [in whom treatment without ribavirin was associated with an 80% SVR_{12}]), but only for 12 weeks and *without* ribavirin in genotype 1b (100% SVR_{12}). For genotype 4, the regimen is given for 12 weeks with ribavirin, but without dasabuvir in treatment-naïve and treatment-experienced patients (100% SVR_{12}), including those with compensated cirrhosis. In July 2016, the FDA approved a long-acting formulation of dasabuvir, allowing once-a-day instead of twice-a-day treatment; for genotype 1a, twice-daily ribavirin dosing remains.

This combination is well tolerated with generally mild side effects, for example, fatigue, asthenia, insomnia, headache, and pruritus. Hyperbilirubinemia (primarily unconjugated) and elevations in alanine aminotransferase activity may occur but resolve during or shortly after treatment. Because of occasional hyperbilirubinemia and potential hepatotoxicity (FDA warning letter issued October 2015 regarding hepatic failure/decompensation reported in treated cirrhotic patients), this combination is not recommended in patients with decompensated cirrhosis, and treated cirrhotic patients should be monitored closely for decompensation; however, the safety and efficacy of this combination have been demonstrated for patients with advanced renal insufficiency. Similar to other regimens containing protease inhibitors, drug-drug interactions are common with other drugs that induce CYP3A4 or are dependent on CYP3A4 for elimination. Checking for potential drug-drug interactions is important prior to initiating therapy with this drug combination (*www.hep-druginteractions.org*). Responsiveness to this multidrug

regimen is not reduced in patients with baseline RASs to these agents.

Compared to sofosbuvir/ledipasvir, this regimen has the disadvantage of requiring twice-a-day ribavirin therapy for genotype 1a and of being contraindicated in decompensated cirrhosis; however, it has the advantage of offering a 12-week, ribavirin-free regimen for prior null responders with cirrhosis and providing an option for patients with renal failure.

Sofosbuvir and Daclatasvir: Daclatasvir, an NS5A inhibitor, along with the polymerase inhibitor sofosbuvir, was approved by the FDA in July 2015 for genotype 3 and in February 2016 for genotype 1 (AASLD-Infectious Diseases Society of America [IDSA] guidelines [see below] include its recommendation as well for genotype 2; in August 2014, this combination was approved in Europe for genotypes 1, 2, 3, and 4, and EASL recommends it for all these genotypes as well as for genotypes 5 and 6). At the time of its approval for genotype 3, daclatasvir filled a need inadequately met by other available combination DAAs. Although data on genotype 3 are the most robust, clinical trials of this combination in genotypes 1 and 2 support its efficacy and recommendations for first-line (genotype 1) and alternative (genotype 2) treatment, in some cases with ribavirin (Table 334-6). Daclatasvir, a 60-mg tablet, and sofosbuvir, a separate 400 mg tablet are taken once-a-day for 12 to 24 weeks.

In clinical trials among treatment-naïve or treatment-experienced patients, SVR_{12} rates for 12 weeks of daclatasvir plus sofosbuvir were 98% with genotype 1 (comparable results in genotypes 1a and 1b), 92% for genotype 2, and 89% for genotype 3. For noncirrhotic patients, the addition of ribavirin or the extension of therapy to 24 weeks did not improve efficacy. In patients with compensated cirrhosis, limited prospective data and data from observational cohorts suggested that extending therapy to 24 weeks, with or without ribavirin, improved efficacy. In cirrhotics, SVR_{12} was achieved in 93% with Child Class-Pugh A and B but in only 56% with Class-C decompensated cirrhosis. For patients with genotype 3 and cirrhosis, the combination was effective in treatment-naïve patients (94% SVR_{12}), but less so in prior nonresponders (69% SVR_{12}). Outcomes in patients with HIV-HCV co-infection were comparable.

Like other sofosbuvir-NS5A inhibitor combinations, daclatasvir plus sofosbuvir is well tolerated (mild fatigue, headache, nausea, diarrhea in 5–14%), but can cause severe bradycardia when administered with amiodarone (contraindicated), especially along with beta blockers. Because daclatasvir is a substrate for CYP3A, CYP3A inducers can reduce daclatasvir levels, and CYP3A inhibitors reduce daclatasvir levels. Similarly, daclatasvir, an inhibitor of P-gp, OATP1B1 and 1B3, and BCP, can increase the levels of drugs that are substrates of these transporters. As noted above for other DAAs, checking for potential drug-drug interactions is advisable prior to initiating therapy (*www.hep-druginteractions.org*). Responsiveness to daclatasvir-containing drug-combination therapy is reduced in cirrhotic patients with genotype 1a and in both cirrhotic and noncirrhotic patients with genotype 3 who have baseline daclatasvir-associated NS5A RASs.

Although daclatasvir-sofosbuvir is approved for genotypes 1 and 3 and recommended as an alternative for genotype 2, better documented efficacy and simplicity of other regimens have limited the popularity of this drug combination.

Elbasvir/Grazoprevir: Elbasvir (50 mg), an NS5A inhibitor, combined in a single, fixed-dose pill with grazoprevir (100 mg), an NS3/4 protease inhibitor, was approved in January 2016 as a once-a-day (with or without food) treatment for genotypes 1 and 4. In clinical trials, a 12-week course was effective in treatment-naïve and treatment-experienced patients without cirrhosis or with compensated cirrhosis. In treatment-naïve patients, this combination yielded an SVR_{12} in 92% of patients with genotype 1a, 99% with genotype 1b, and 100% with genotype 4 (very small numbers, however); 10 patients with genotype 6 were included, but only 80% achieved SVR_{12}. Cirrhotic and noncirrhotic patients had comparable rates of SVR_{12}, 97% and 94%, respectively. For this drug combination, however, ~11% of patients with genotype 1a harbor NS5A polymorphisms, that is, RASs, at baseline. If present, these NS5A RASs reduce efficacy of elbasvir/grazoprevir (unlike baseline RASs to the most of the other combination DAA regimens described above and below) from 99% to 58% in treatment-naïve patients. Therefore, all patients with genotype 1a require baseline RAS testing; if these RASs are present, treatment extension to 16 weeks and the addition of weight-based ribavirin bring the SVR_{12} up to expected levels of close to 100%. In treatment-experienced patients, both extending treatment to 16 weeks and adding ribavirin were studied; however, generally, in the absence of baseline NS5A RASs, SVR_{12} rates were not increased over those without ribavirin for 12 weeks (94–97%). For genotype 1a, among prior nonresponders to PEG IFN/ribavirin, 12 weeks of elbasvir/grazoprevir suffices without ribavirin except for patients with baseline NS5A RASs, who require 16 weeks of therapy and ribavirin. Among nonresponders to prior protease-inhibitor therapy, even in the absence of baseline NS5A RASs, ribavirin should be added to a 12-week regimen; in the presence of baseline NS5A RASs, treatment should be extended to 16 weeks and ribavirin added. For genotype 1b, NS5A RASs are not an issue, and the only subgroup requiring modification of a 12-week course of therapy are prior nonreponders to protease-inhibitor regimens, for whom ribavirin is added. For genotype 4, the recommended regimen for all prior nonresponders (whether to PEG IFN/ribavirin or protease inhibitor regimens) is 16 weeks of elbasvir/grazoprevir plus ribavirin (Table 334-6).

This combination is just as effective in patients with HIV-HCV co-infection and in patients with advanced renal failure (including those requiring hemodialysis); however, it is contraindicated in decompensated cirrhosis. Like other protease inhibitor regimens, elbasvir/grazoprevir can be associated with aminotransferase elevations and potential hepatotoxicity; because these drugs are excreted by the liver, in decompensated liver disease, plasma drug concentrations may become elevated substantially. Therefore, all treated patients should have alanine aminotransferase screening periodically during therapy, and the drug should be stopped for elevations exceeding 10-fold or for elevations of conjugated bilirubin, alkaline phosphatase, or prothrombin time.

Elbasvir/grazoprevir is well tolerated, with only low levels of mild adverse effects (fatigue, headache, nausea in 5–11%) seen just as frequently in placebo recipients. Both elbasvir and grazoprevir are substrates for CYP3A and are subject to multiple potential drug-drug interactions. Therefore, this combination should not be used with potent CYP3A inducers; conversely, CYP3A and OATP1B1 inhibitors can lead to untoward elevations of plasma elbasvir/grazoprevir concentrations. Checking for potential drug-drug interactions is advisable prior to initiating therapy (*www.hep-druginteractions.org*).

Compared to other available regimens for genotypes 1 and 4, elbasvir/grazoprevir has the disadvantage/inconvenience of requiring baseline NS5A RAS testing but the advantages of a comparable regimen for cirrhotics and noncirrhotics, for treatment-naïve and treatment-experienced patients, and for patients with normal renal function and with renal failure.

Sofosbuvir/velpatasvir: The combination in a single, fixed-dose pill of velpatasvir (100 mg), a highly potent, pangenotypic NS5A inhibitor, along with the polymerase inhibitor sofosbuvir (400 mg) was approved in June 2016 for genotypes 1–6, in treatment-naïve and treatment-experienced noncirrhotics and cirrhotics. Ribavirin is not required, including in patients with genotypes 2 and 3, except in patients with decompensated cirrhosis.

In a series of clinical trials, this combination for 12 weeks in the absence of ribavirin was shown to yield 99% SVR_{12} (range 97–100%) in genotypes 1, 2, 4, 5, and 6 and 95% in genotype 3. Baseline NS5A RASs had no impact on responsiveness.

Prior to the availability of this drug combination, patients with genotype 3, especially those with cirrhosis and prior null response to other therapies, proved to be the most refractory subset of patients. In treatment-naïve patients with genotype 3, 12 weeks of sofosbuvir/velpatasvir (95% SVR_{12}) was superior to 24 weeks of sofosbuvir plus ribavirin (80% SVR_{12}). In patients with genotype 3, the combination of sofosbuvir/velpatasvir for 12 weeks was comparable in noncirrhotics (97% SVR_{12}) and cirrhotics (91% SVR_{12}) and in

treatment-naïve (97% SVR_{12}) and treatment-experienced (90% SVR_{12}) patients, superior in all these categories to 24 weeks of sofosbuvir plus ribavirin (87%, 66%, 86%, and 63%, respectively). In cirrhotic null responders, most available IFN-free regimens for genotype 3 (including daclatasvir plus sofosbuvir, approved specifically for this genotype) achieved SVR_{12} rates in the range of ~60–75%, while the combination of PEG IFN, ribavirin, and sofosbuvir could boost SVR_{12} to the mid-80% range. For treatment-experienced patients with genotype 3, sofosbuvir/velpatasvir in noncirrhotics and cirrhotics had similarly high efficacy (91% and 89% SVR_{12}, respectively); this was the highest recorded SVR_{12} for genotype-3 cirrhotic null responders treated with IFN-free DAA regimens. Finally, in patients with genotypes 1–4 and 6 and with decompensated, Class-B cirrhosis (55% treatment-experienced), sofosbuvir/velpatasvir plus ribavirin for 12 weeks yielded an SVR_{12} in 94%; this result was better than sofosbuvir/velpatasvir without ribavirin for 12 weeks (83% SVR_{12}) or 24 weeks (86% SVR_{12}).

Like other all-oral DAAs, sofosbuvir/velpatasvir was very well tolerated; in noncirrhotic and compensated cirrhotic patients, mild headache and fatigue was seen in >10%—this occurred in a comparable proportion of placebo recipients; in decompensated cirrhosis, mild fatigue, headache, nausea, insomnia, diarrhea, and anemia (ribavirin was part of the regimen) was seen in >10%. Like other sofosbuvir-containing regimens, sofosbuvir/velpatasvir should not be administered along with amiodarone (potential serious bradycardia); in addition, P-gp inducers and moderate-to-potent CYP3A inducers can reduce plasma levels of sofosbuvir and/or velpatasvir. Checking for drug-drug interactions prior to therapy is advisable (*www.hep-druginteractions.org*). Baseline RASs do not influence responsiveness to this combination.

FUTURE DIRECT-ACTING ANTIVIRAL COMBINATION THERAPY (2017–)

Most treatment needs have been met by contemporary DAA regimens described above; however, several additional, highly potent, pangenotypic drug combinations are in development. For example, an investigative protease inhibitor (voxilaprevir) added to the polymerase inhibitor/NS5A inhibitor combination of sofosbuvir/velpatasvir yields a very well tolerated *triple-drug* combination with 97% SVR_{12} across all HCV genotypes and patient subgroups. These include noncirrhotic/cirrhotic, treatment-naïve/treatment-experienced groups, including those who had prior NS5A treatment and results were independent of the number of prior DAA drug classes received; no effects of baseline NS5A RASs were noted. Several experimental combinations may allow even briefer durations of therapy. In a small, exploratory trial, a *6-week* combination of sofosbuvir plus an experimental pangenotypic, very high potency, very low resistance NS5A inhibitor (odalasvir) achieved SVR_{12} in 100% of 12 patients with genotype 1. Similarly, in a *6-week* triple combination of odalasvir with the protease inhibitor simeprevir and an experimental polymerase inhibitor ("AL-335"), SVR_{12} was observed in 100% of 20 treatment-naïve noncirrhotic patients with genotype 1. In phase-II clinical trials, *8 weeks* of an experimental combination of two high-potency, pangenotypic DAAs, a protease inhibitor ("ABT-493") plus an NS5A inhibitor ("ABT-530"), yielded 100% SVR_{12} in treatment-naïve noncirrhotic patients with genotypes 1, 2, and 3. In cirrhotics with genotype 3 and in patients with genotypes 4, 5, and 6, 12 weeks of therapy with this DAA combination yielded 100% SVR_{12}. In patients with prior DAA treatment failure, 12 weeks of this double-combination sufficed to achieve a ≥95% SVR_{12}; neither baseline NS5A nor protease inhibitor RASs influenced SVR_{12} rates. No safety issues have been encountered, and the potential for drug-drug interactions is limited. These promising combinations are undergoing phase-II and phase-III trials.

Less advanced is the development of inhibitors of host proteins, such as oral, nonimmunosuppressive inhibitors of cyclophilin A (which interacts with NS5A during HCV replication) and subcutaneous antisense antagonists of host liver-expressed micro-RNA-122 (which promotes HCV replication). Given the accelerated progress of all-oral, short-treatment-duration, high-efficacy, DAAs, these alternative approaches may not be practical or competitive; moreover, development of both approaches has been retarded by emerging toxicities such as pancreatitis associated with cyclophilin inhibitors and jaundice associated with micro-RNA-122.

Although data on the impact of DAAs on the natural history of chronic hepatitis C are still limited, preliminary findings are that successful therapy is associated with a gradual reduction in fibrosis progression and a regression of advanced fibrosis (cirrhosis), improvement in survival among patients with decompensated cirrhosis, and a decline in the number of patients with hepatitis C being referred for liver transplantation. Based on the known prevalence, natural history, and rate of progression of chronic hepatitis C and on the efficacy of DAA therapies and their impact on the complications of hepatitis C, modeling estimates have suggested that the availability and application of these therapies have the potential to reduce the hepatitis C-associated disease burden including liver-related death, HCC, decompensated cirrhosis, and liver transplantation by 50–70% between 2015 and 2050.

TREATMENT RECOMMENDATIONS

Because the pace of new drug development and approval has been so rapid, the AASLD and the IDSA have been providing a consensus of updated treatment recommendations for patients with hepatitis C; these recommendations, which continue to be revised regularly based on new data, are available online at *www.hcvguidelines.org* and should be consulted before initiating therapy (Table 334-6). The EASL issues similar (but not identical) treatment recommendations annually for hepatitis C (*www.easl.eu*), most recently in September 2016. Divergences between AASLD-IDSA and EASL recommendations are noted in Table 334-6.

Prior to therapy, HCV genotype should be determined, because the genotype dictates which treatment regimens are indicated (Table 334-6). Monitoring of serum HCV RNA levels pretreatment, during treatment, and posttreatment is crucial in assessing response to therapy; moreover, the baseline level may contribute to determining the duration of therapy (e.g., in noncirrhotic patients with genotype 1 and HCV RNA $<6 \times 10^6$ IU/mL, 8 [instead of the usual 12] weeks of sofosbuvir/ledipasvir may be a consideration). The goal of treatment is to eradicate HCV RNA during therapy and to document that the virus remains undetectable for at least 12 weeks after completion of therapy (SVR_{12}). Several reports have appeared describing hepatitis B reactivation, often severe, during and after DAA therapy in patients coinfected with HCV and HBV who were not being treated for their HBV infections. Therefore, screening for HBV infection is recommended prior to initiating DAA therapy for hepatitis C (which should have been done to determine HBV-immunity status as a prelude to recommended hepatitis B vaccination in patients with chronic hepatitis C), and therapy for HBV infection (for those meeting HBV treatment criteria, see above) should be initiated prior to or simultaneously with HCV therapy.

INDICATIONS FOR ANTIVIRAL THERAPY

Patients with chronic hepatitis C who have detectable HCV RNA in serum, whether or not aminotransferase levels are increased, and chronic hepatitis of any grade and stage are candidates for antiviral therapy with DAA agents. The only exception would be patients with short life expectancies, for whom treating hepatitis C would have no influence on longevity. Certainly, for patients with advanced liver disease, early treatment merits a high priority. Although patients with persistently normal aminotransferase activity tend to progress histologically very slowly or not at all, they respond to antiviral therapy just as well as do patients with elevated aminotransferase levels; therefore, such patients are potential candidates for antiviral therapy. As noted above, antiviral therapy has been shown to improve survival and complication-free survival and to slow progression of and to reverse fibrosis.

HCV genotype determines the regimen to be selected (Table 334-6). Similarly, the absence or presence of cirrhosis/advanced fibrosis determines the treatment options from which to select, including

the antiviral agents to be used, the duration of therapy, and the need for ribavirin (Table 334-6). A pretreatment liver biopsy to assess histologic grade and stage provides substantial information about progression of hepatitis C in the past, has prognostic value for future progression, and can identify such histologic factors as steatosis and stage of fibrosis, which can influence responsiveness to therapy. As therapy has improved for patients with a broad range of histologic severity, and as noninvasive measures of the stage of fibrosis (e.g., assessment of liver elasticity by imaging) have gained in accuracy and popularity, noninvasive approaches have supplanted histology in most cases. If cirrhosis/advanced fibrosis is present prior to therapy, the risk of HCC, although reduced substantially by successful therapy, is not eliminated, and twice yearly posttreatment imaging for HCC surveillance (and endoscopic surveillance for esophageal varices at intervals of 1–3 years) is indicated even after an SVR. In patients with low-level fibrosis at baseline, achievement of an SVR allows the cessation of such surveillance.

Patients who have relapsed after, or failed to respond to, a course of IFN-based or DAA agent-based therapy are candidates for retreatment with a DAA therapy regimen (Table 334-6). For patients who have failed to respond to a DAA combination, options include increasing the duration of therapy with the failed regimen, adding ribavirin, or changing the drug class (e.g., after failed protease and polymerase inhibitors, switching to an NS5A-containing combination). In the presence of cirrhosis or a need for urgent retreatment, patients who have failed protease inhibitor plus polymerase inhibitor combination therapy or who have failed an NS5A combination are candidates for RAS testing and tailored therapy based on such resistance testing. If reliable RAS testing is not available, adding ribavirin or extending the duration of therapy are options. For prior nonresponders to IFN-based therapy, NS5A inhibitor-containing regimens are highly effective; however, reduced responsiveness can be encountered, especially in cirrhotic patients. For this relatively refractory group, ideally, the most potent/effective NS5A regimen should be selected to give such patients the best chance of responding and to avoid treatment-emergent NS5A RASs. Additional details for treatment of such patient subgroups can be found at *www.hcvguidelines.org*.

Persons with acute hepatitis C are also candidates for antiviral therapy (**Chap. 332**) with the same DAA agents approved for chronic hepatitis C; delaying the initiation of therapy for an observation period of 12–16 weeks (and even up to 6 months) has been recommended to allow for spontaneous recovery, especially in light of the fact that most cases of acute hepatitis C are not clinically severe or rapidly progressive. The duration of therapy for acute hepatitis C has not been determined definitively; however, in a small study of 20 patients, 6 weeks of sofosbuvir/ledipasvir sufficed for a 100% SVR_{12}. According to 2016 EASL recommendations, patients with acute hepatitis C should be treated for 8 weeks with a genotype-appropriate DAA regimen consisting of sofosbuvir plus one of the three approved NS5A inhibitors without ribavirin (extended to 12 weeks for patients with acute hepatitis C and HIV co-infection or for patients with acute hepatitis C and a baseline HCV RNA level >1 million IU/mL). In patients with biochemically and histologically mild chronic hepatitis C, the rate of progression is slow; however, such patients respond just as well to antiviral therapy as those with elevated aminotransferase levels and more histologically severe hepatitis. Because of the high cost of DAA treatments, initially a higher priority was assigned to patients with advanced fibrosis/cirrhosis; however, this controversial approach was relied upon by some medical insurers and pharmacy benefit management organizations to withhold therapy from patients with low-level fibrosis. Unfortunately, delaying therapy until fibrosis becomes advanced misses the opportunity to prevent all the dire consequences of chronic hepatitis C (liver failure, death/transplantation, HCC), which can be reduced, but not eliminated completely once advanced fibrosis is established. Therefore, therapy for patients with mild disease is justified as well as cost-effective.

Patients with compensated cirrhosis can respond to therapy, and their likelihood of a sustained response with DAAs is comparable to that in noncirrhotics. Patients with decompensated cirrhosis, who were not candidates for IFN-based antiviral therapy, respond well to DAA therapy regimens consisting of combinations of polymerase inhibitors and NS5A inhibitors (e.g., sofosbuvir/ledipasvir, sofosbuvir/velpatasvir); however, protease-inhibitor-containing combinations have been associated with potential hepatotoxicity and hepatic decompensation and are contraindicated in this patient subset. Patients with decompensated cirrhosis should be referred to a liver transplantation center. DAAs are highly effective not only for patients with end-stage liver disease awaiting liver transplantation but also for patients with recurrent hepatitis C after liver transplantation. Ideally, patients should be treated prior to liver transplantation; however, a concern is that eradication of HCV infection will disqualify such patients from accepting donor livers from persons with HCV infection, thus contracting the potential donor pool and limiting accessibility to donor organs and timely transplantation. In addition, responsiveness to DAA therapy appears to be reduced in patients with decompensated cirrhosis and with high model for end-stage liver disease (MELD) scores; in this subgroup, responsiveness after liver transplantation would be substantially better. Therefore, advocacy has been expressed (recommended by EASL) for postponing DAA therapy in patients with high-MELD HCV-associated end-stage liver disease until after liver transplantation; the decision whether to treat pretransplantation or posttransplantation should be individualized thoughtfully for each patient, based on such factors as MELD score, time anticipated prior to availability of a donor organ, relative clinical stability, and co-morbidities **(Chap. 338)**. The cutaneous and renal vasculitis of HCV-associated essential mixed cryoglobulinemia **(Chap. 332)** may respond to antiviral therapy, but sustained responses were rare after discontinuation of therapy in the IFN era, and prolonged, potentially indefinite, therapy was recommended. Now that more effective DAAs are available, a 12-week course of sofosbuvir-based combination therapy has been shown to yield an SVR_{12} rate exceeding 80% in cryoglobulinemic vasculitis. Anecdotal reports suggest that IFN-based antiviral therapy may be effective in porphyria cutanea tarda or lichen planus associated with hepatitis C; whether the more appealing DAAs are effective in these groups remains to be documented.

In patients with HCV/HIV co-infection, hepatitis C is more progressive and severe than in HCV-monoinfected patients. Although patients with HCV/HIV co-infection responded less well to IFN-based antiviral therapy for hepatitis C, they respond as well as patients with HCV infection alone to DAA combination regimens. In HCV/HIV-infected patients, ribavirin can potentiate the toxicity of didanosine (e.g., lactic acidosis) and the lipoatrophy of stavudine, and zidovudine can exacerbate ribavirin-associated hemolytic anemia; therefore, these drug combinations should be avoided.

Patients with a history of injection drug use and alcoholism can be treated successfully for chronic hepatitis C, preferably in conjunction with drug and alcohol treatment programs. Moreover, because injection-drug users, as a source of transmission to others, account disproportionately for perpetuating the spread of HCV infection in the population, the impact of treating active injection-drug users is amplified by reducing such transmission. The approved oral combinations of DAAs are effective in patients with mild-modest renal failure and require no dose adjustments; however, in patients with severe renal impairment (creatinine clearances <30 mL/minute), data are limited on the use of sofosbuvir-containing combinations. For such patients, including those undergoing hemodialysis, recommended combinations are 12 weeks of elbasvir/grazoprevir for genotypes 1a, 1b, and 4 or 12 weeks of paritaprevir/ritonavir, ombitasvir, and dasabuvir for genotype 1b. In genotype 1a, the addition of 200 mg/day of ribavirin to paritaprevir/ritonavir, ombitasvir, and dasabuvir, if the hemoglobin level exceeds 10 g/dL, is an alternative regimen but requires vigilance for the onset of ribavirin-induced hemolytic anemia. For patients with severe renal impairment and HCV genotypes 2, 3, 5, or 6, PEG IFN with low-dose ribavirin (200 mg daily, if the hemoglobin exceeds 10 g/dL) is recommended. After renal transplantation, levels of SVR_{12} in patients treated with the approved oral DAA combinations have approached 100%.

No clinical studies of the use of DAAs during pregnancy are available. Ribavirin is contraindicated during pregnancy; therefore, any regimen including ribavirin should not be used. Sofosbuvir; sofosbuvir + ledipasvir; and paritaprevir/ritonavir, ombitasvir, and dasabuvir are classified as pregnancy category B; the other DAAs do not have a pregnancy classification. Therefore, these therapies are not indicated routinely in pregnancy and should be used, with caution, only if the benefit of treatment is compelling and justified compared to the potential for fetal risk.

Choosing among available treatment options: The large number of recommended all-oral DAA combinations can be daunting to treating clinicians. In some instances, the combination approved is determined by insurance payers; however, cost considerations aside, how is the clinician to choose among the options? The most popular of the regimens has been fixed-dose, single-pill sofosbuvir/ledipasvir, which is effective for all genotypes except 2 and 3, which requires no baseline RAS testing, and which can be used in noncirrhotic patients with genotype 1 and low-level viremia for as brief a period as 8 weeks. For genotypes 2 and 3, fixed-dose, single-pill sofosbuvir/velpatasvir appears to be the combination of choice; because this combination is so effective across all genotypes, in the future, for simplicity, clinicians may resort to a "one-size-fits-all" regimen such as this one in all patients (except for those with advanced renal failure). In addition, this regimen is the only one that can be used in almost all situations (independent of genotype, treatment experience, and cirrhosis) without ribavirin, and the duration of which is almost always 12 weeks; exceptions: (a) ribavirin recommended for decompensated cirrhosis, (b) EASL recommends adding ribavirin in treatment-experienced patients with genotype 3 or, if ribavirin is contraindicated, extending treatment to 24 weeks (Table 334-6, footnote c). As noted above, protease-inhibitor-containing DAA regimens (elbasvir/grazoprevir; paritaprevir/ritonavir, ombitasvir, and dasabuvir; simeprevir and sofosbuvir) are contraindicated in decompensated cirrhosis. For advanced renal failure, safety and efficacy have been documented for elbasvir/grazoprevir and paritaprevir/ritonavir, ombitasvir, and dasabuvir, but not for sofosbuvir-NS5A combinations.

AUTOIMMUNE HEPATITIS

DEFINITION

Autoimmune hepatitis is a chronic disorder characterized by continuing hepatocellular necrosis and inflammation, usually with fibrosis, which can progress to cirrhosis and liver failure. When fulfilling criteria of severity, this type of chronic hepatitis, when untreated, may have a 6-month mortality of as high as 40%. Based on contemporary estimates of the natural history of autoimmune hepatitis, the 10-year survival is 80–98% for treated and 67% for untreated patients. The prominence of extrahepatic features of autoimmunity and seroimmunologic abnormalities in this disorder supports an autoimmune process in its pathogenesis; this concept is reflected in the prior labels *lupoid* and *plasma cell hepatitis*. Autoantibodies and other typical features of autoimmunity, however, do not occur in all cases; among the broader categories of "idiopathic" or cryptogenic chronic hepatitis, many, perhaps the majority, are probably autoimmune in origin. Cases in which hepatotropic viruses, metabolic/genetic derangements (including nonalcoholic fatty liver disease), and hepatotoxic drugs have been excluded represent a spectrum of heterogeneous liver disorders of unknown cause, a proportion of which are most likely autoimmune hepatitis.

IMMUNOPATHOGENESIS

The weight of evidence suggests that the progressive liver injury in patients with autoimmune hepatitis is the result of a cell-mediated immunologic attack directed against liver cells in the setting of a loss of, or failed, immunologic tolerance for self liver antigens. In all likelihood, predisposition to autoimmunity is inherited, whereas the liver specificity of this injury is triggered by environmental (e.g., chemical, drug [e.g., minocycline], or viral) factors. For example, patients have been described in whom apparently self-limited cases of acute hepatitis A, B, or C led to autoimmune hepatitis, presumably because of genetic susceptibility or predisposition. Evidence to support an autoimmune pathogenesis in this type of hepatitis includes the following: (1) in the liver, the histopathologic lesions are composed predominantly of cytotoxic T cells and plasma cells; (2) circulating autoantibodies (nuclear, smooth muscle, thyroid, etc.; see below), rheumatoid factor, and hyperglobulinemia are common; (3) other autoimmune disorders—such as autoimmune thyroiditis, rheumatoid arthritis, autoimmune hemolytic anemia, ulcerative colitis, membranoproliferative glomerulonephritis, juvenile diabetes mellitus, vitiligo, celiac disease, and Sjögren's syndrome—occur with increased frequency in patients and in their relatives who have autoimmune hepatitis; (4) histocompatibility haplotypes associated with autoimmune diseases, such as HLA-B1, B8, DR3, and DR4 as well as extended haplotype *DRB1*0301* and *DRB1*0401* alleles, are common in patients with autoimmune hepatitis; and (5) this type of chronic hepatitis is responsive to glucocorticoid/immunosuppressive therapy, effective in a variety of autoimmune disorders.

Cellular immune mechanisms appear to be important in the pathogenesis of autoimmune hepatitis. In vitro studies have suggested that in patients with this disorder, $CD4^+$ T lymphocytes are capable of becoming sensitized to hepatocyte membrane proteins and of destroying liver cells. Molecular mimicry by cross-reacting antigens that contain epitopes similar to liver antigens is postulated to activate these T cells, which infiltrate, and result in injury to, the liver. Abnormalities of immunoregulatory control over cytotoxic lymphocytes (impaired regulatory CD4+CD25+ T cell influences) may play a role as well. Studies of genetic predisposition to autoimmune hepatitis demonstrate that certain haplotypes are associated with the disorder, as enumerated above, as are polymorphisms in cytotoxic T lymphocyte antigens (*CTLA-4*) and tumor necrosis factor α (*TNFA*2*). The precise triggering factors, genetic influences, and cytotoxic and immunoregulatory mechanisms involved in this type of liver injury remain incompletely defined.

Intriguing clues into the pathogenesis of autoimmune hepatitis come from the observation that circulating autoantibodies are prevalent in patients with this disorder. Among the autoantibodies described in these patients are antibodies to nuclei (so-called antinuclear antibodies [ANAs], primarily in a homogeneous pattern) and smooth muscle (so-called anti-smooth-muscle antibodies, directed at actin, vimentin, and skeletin), antibodies to F-actin, anti-LKM (see below), antibodies to "soluble liver antigen" (directed against a uracil-guanine-adenine transfer RNA suppressor protein), antibodies to α-actinin, and antibodies to the liver-specific asialoglycoprotein receptor (or "hepatic lectin") and other hepatocyte membrane proteins. Although some of these provide helpful diagnostic markers, their involvement in the pathogenesis of autoimmune hepatitis has not been established.

Humoral immune mechanisms have been shown to play a role in the extrahepatic manifestations of autoimmune and idiopathic hepatitis. Arthralgias, arthritis, cutaneous vasculitis, and glomerulonephritis occurring in patients with autoimmune hepatitis appear to be mediated by the deposition of circulating immune complexes in affected tissue vessels, followed by complement activation, inflammation, and tissue injury. While specific viral antigen-antibody complexes can be identified in acute and chronic viral hepatitis, the nature of the immune complexes in autoimmune hepatitis has not been defined.

CLINICAL FEATURES

Many of the *clinical features* of autoimmune hepatitis are similar to those described for chronic viral hepatitis. The onset of disease may be insidious or abrupt; the disease may present initially like, and be confused with, acute viral hepatitis; a history of recurrent bouts of what had been labeled *acute hepatitis* is not uncommon. In approximately a quarter of patients, the diagnosis is made in the absence of symptoms, based on abnormal liver laboratory tests. A subset of patients with autoimmune hepatitis has distinct features. Such patients are predominantly young to middle-aged women with marked hyperglobulinemia and high-titer circulating ANAs. This is the group with positive lupus erythematosus (LE) preparations (initially labeled "*lupoid*" hepatitis) in whom other autoimmune features are common. Fatigue, malaise,

anorexia, amenorrhea, acne, arthralgias, and jaundice are common. Occasionally, arthritis, maculopapular eruptions (including cutaneous vasculitis), erythema nodosum, colitis, pleurisy, pericarditis, anemia, azotemia, and sicca syndrome (keratoconjunctivitis, xerostomia) occur. In some patients, complications of cirrhosis, such as ascites and edema (associated with portal hypertension and hypoalbuminemia), encephalopathy, hypersplenism, coagulopathy, or variceal bleeding may bring the patient to initial medical attention.

The course of autoimmune hepatitis may be variable. In patients with mild disease or limited histologic lesions (e.g., piecemeal necrosis without bridging), progression to cirrhosis is limited, but, even in this subset, clinical monitoring is important to identify progression; up to half left untreated can progress to cirrhosis over the course of 15 years. In North America, cirrhosis at presentation is more common in African Americans than in whites. In those with severe symptomatic autoimmune hepatitis (aminotransferase levels >10 times normal, marked hyperglobulinemia, "aggressive" histologic lesions—bridging necrosis or multilobular collapse, cirrhosis), the 6-month mortality without therapy may be as high as 40%. Such severe disease accounts for only 20% of cases; the natural history of milder disease is variable, often accentuated by spontaneous remissions and exacerbations. Especially poor prognostic signs include the presence histologically of multilobular collapse at the time of initial presentation and failure of serum bilirubin to improve after 2 weeks of therapy. Death may result from hepatic failure, hepatic coma, other complications of cirrhosis (e.g., variceal hemorrhage), and intercurrent infection. In patients with established cirrhosis, HCC may be a late complication **(Chap. 78)** but occurs less frequently than in cirrhosis associated with viral hepatitis.

Laboratory features of autoimmune hepatitis are similar to those seen in chronic viral hepatitis. Liver biochemical tests are invariably abnormal but may not correlate with the clinical severity or histopathologic features in individual cases. Many patients with autoimmune hepatitis have normal serum bilirubin, alkaline phosphatase, and globulin levels with only minimal aminotransferase elevations. Serum AST and ALT levels are increased and fluctuate in the range of 100–1000 units. In severe cases, the serum bilirubin level is moderately elevated (51–171 μmol/L [3–10 mg/dL]). Hypoalbuminemia occurs in patients with very active or advanced disease. Serum alkaline phosphatase levels may be moderately elevated or near normal. In a small proportion of patients, marked elevations of alkaline phosphatase activity occur; in such patients, clinical and laboratory features overlap with those of primary biliary cirrhosis **(Chap. 337)**. The prothrombin time is often prolonged, particularly late in the disease or during active phases.

Polyclonal hypergammaglobulinemia (>2.5 g/dL) is common in autoimmune hepatitis, as is the presence of rheumatoid factor. As noted above, circulating autoantibodies are also prevalent, most characteristically ANAs in a homogeneous staining pattern. Smooth-muscle antibodies are less specific, seen just as frequently in chronic viral hepatitis. Because of the high levels of globulins achieved in the circulation of some patients with autoimmune hepatitis, occasionally the globulins may bind nonspecifically in solid-phase binding immunoassays for viral antibodies. This has been recognized most commonly in tests for antibodies to hepatitis C virus, as noted above. In fact, studies of autoantibodies in autoimmune hepatitis have led to the recognition of new categories of autoimmune hepatitis. *Type I autoimmune hepatitis* is the classic syndrome prevalent in North America and northern Europe occurring in young women, associated with marked hyperglobulinemia, lupoid features, circulating ANAs, and HLA-DR3 or HLA-DR4 (especially *B8-DRB1*03*). Also associated with type I autoimmune hepatitis are autoantibodies against actin and atypical perinuclear antineutrophilic cytoplasmic antibodies (pANCA). Included in the spectrum of type-I autoimmune hepatitis is a subset of patients who lack ANA and anti-LKM1, but who have circulating antibodies to soluble liver antigen. Most of these patients are women and have clinical features similar to, perhaps more severe than, those of other patients with type I autoimmune hepatitis.

Type II autoimmune hepatitis, often seen in children, more common in Mediterranean populations, and linked to HLA- DRB1 and HLA-DQB1 haplotypes, is associated not with ANA but with anti-LKM. Actually, anti-LKM represent a heterogeneous group of antibodies. In type II autoimmune hepatitis, the antibody is anti-LKM1, directed against cytochrome P450 2D6. This is the same anti-LKM seen in some patients with chronic hepatitis C. Anti-LKM2 is seen in drug-induced hepatitis, and anti-LKM3 (directed against uridine diphosphate glucuronyltransferases) is seen in patients with chronic hepatitis D. Another autoantibody observed in type II autoimmune hepatitis is directed against liver cytosol formiminotransferase cyclodeaminase (anti-liver cytosol 1).

Liver biopsy abnormalities are similar to those described for chronic viral hepatitis. Expanding portal tracts and extending beyond the plate of periportal hepatocytes into the parenchyma (designated *interface hepatitis* or *piecemeal necrosis*) is a mononuclear cell infiltrate that, in autoimmune hepatitis, may include the presence of plasma cells. Necroinflammatory activity characterizes the lobular parenchyma, and evidence of hepatocellular regeneration is reflected by "rosette" formation, the occurrence of thickened liver cell plates, and regenerative "pseudolobules." Septal fibrosis, bridging fibrosis, and cirrhosis are frequent. In patients with early autoimmune hepatitis presenting as an acute-hepatitis-like illness, lobular and centrilobular (as opposed to the more common periportal) necrosis has been reported. Bile duct injury and granulomas are uncommon; however, a subgroup of patients with autoimmune hepatitis has histologic, biochemical, and serologic features overlapping those of primary biliary cirrhosis **(Chap. 337)**.

DIAGNOSTIC CRITERIA

An international group has suggested a set of criteria for establishing a diagnosis of autoimmune hepatitis. Exclusion of liver disease caused by genetic disorders, viral hepatitis, drug hepatotoxicity, and alcohol are linked with such inclusive diagnostic criteria as hyperglobulinemia, autoantibodies, and characteristic histologic features. This international group has also suggested a comprehensive diagnostic scoring system that, rarely required for typical cases, may be helpful when typical features are not present. Factors that weigh in favor of the diagnosis include female gender; predominant aminotransferase elevation; presence and level of globulin elevation; presence of nuclear, smooth muscle, LKM1, and other autoantibodies; concurrent other autoimmune diseases; characteristic histologic features (interface hepatitis, plasma cells, rosettes); HLA-DR3 or DR4 markers; and response to treatment (see below). A more simplified, more specific scoring system relies on four variables: autoantibodies, serum IgG level, typical or compatible histologic features, and absence of viral hepatitis markers. Weighing against the diagnosis are predominant alkaline phosphatase elevation, mitochondrial antibodies, markers of viral hepatitis, history of hepatotoxic drugs or excessive alcohol, histologic evidence of bile duct injury, or such atypical histologic features as fatty infiltration, iron overload, and viral inclusions.

DIFFERENTIAL DIAGNOSIS

Early during the course of chronic hepatitis, autoimmune hepatitis may resemble typical *acute viral hepatitis* **(Chap. 332)**. Without histologic assessment, severe chronic hepatitis cannot be readily distinguished based on clinical or biochemical criteria from mild chronic hepatitis. In adolescence, *Wilson's disease* **(Chaps. 337 and 408)** may present with features of chronic hepatitis long before neurologic manifestations become apparent and before the formation of Kayser-Fleischer rings (copper deposition in Descemet's membrane in the periphery of the cornea). In this age group, serum ceruloplasmin and serum and urinary copper determinations plus measurement of liver copper levels establish the correct diagnosis. *Postnecrotic* or *cryptogenic cirrhosis* and *primary biliary cirrhosis* **(Chap. 337)** share clinical features with autoimmune hepatitis, and both alcoholic hepatitis **(Chap. 335)** and nonalcoholic steatohepatitis **(Chap. 336)** may present with many features common to autoimmune hepatitis; historic, biochemical, serologic, and histologic assessments are usually sufficient to allow these entities to be distinguished from autoimmune hepatitis. Of course, the distinction between autoimmune and chronic viral hepatitis is not always straightforward, especially when viral antibodies occur in patients with autoimmune disease or when autoantibodies occur in patients with viral disease. Furthermore, the presence of extrahepatic features such as arthritis, cutaneous vasculitis, or pleuritis—not to

mention the presence of circulating autoantibodies—may cause confusion with *rheumatologic disorders* such as rheumatoid arthritis and systemic LE. The existence of clinical and biochemical features of progressive necroinflammatory liver disease distinguishes chronic hepatitis from these other disorders, which are not associated with severe liver disease. Rarely, hepatic venous outflow obstruction (Budd-Chiari syndrome) may present with features suggestive of autoimmune hepatitis, but painful hepatomegaly, ascites, and vascular imaging provide distinguishing diagnostic clues. Other diagnostic considerations would include celiac disease and ischemic liver disease, which would be readily distinguishable by clinical and laboratory features from autoimmune hepatitis.

Finally, occasionally, features of autoimmune hepatitis overlap with features of autoimmune biliary disorders such as primary biliary cirrhosis, primary sclerosing cholangitis **(Chaps. 337 and 339)**, or, even more rarely, mitochondrial antibody-negative autoimmune cholangitis. Such overlap syndromes are difficult to categorize, and often response to therapy may be the distinguishing factor that establishes the diagnosis.

TREATMENT

Autoimmune Hepatitis

The mainstay of management in autoimmune hepatitis is glucocorticoid therapy. Several controlled clinical trials have documented that such therapy leads to symptomatic, clinical, biochemical, and histologic improvement as well as increased survival. A therapeutic response can be expected in up to 80% of patients. Unfortunately, therapy has not been shown in clinical trials to prevent ultimate progression to cirrhosis; however, instances of reversal of fibrosis and cirrhosis have been reported in patients responding to treatment, and rapid treatment responses within 1 year do translate into a reduction in progression to cirrhosis. Although some advocate the use of prednisolone (the hepatic metabolite of prednisone), prednisone is just as effective and is favored by most authorities. Therapy may be initiated at 20 mg/d, but a popular regimen in the United States relies on an initiation dose of 60 mg/d. This high dose is tapered successively over the course of a month down to a maintenance level of 20 mg/d. An alternative, but equally effective, more appealing approach is to begin with half the prednisone dose (30 mg/d) along with azathioprine (50 mg/d). With azathioprine maintained at 50 mg/d, the prednisone dose is tapered over the course of a month down to a maintenance level of 10 mg/d. The advantage of the combination approach is a reduction, over the span of an 18-month course of therapy, in serious, life-threatening complications of steroid therapy (e.g., cushingoid features, hypertension, diabetes, osteoporosis) from 66% down to under 20%. Genetic analysis for thiopurine S-methyltransferase allelic variants does not correlate with azathioprine-associated cytopenias or efficacy and is not assessed routinely in patients with autoimmune hepatitis. In combination regimens, 6-mercaptopurine may be substituted for its prodrug azathioprine, but this is rarely required. Azathioprine alone, however, is not effective in achieving remission, nor is alternate-day glucocorticoid therapy. Limited experience with budesonide in noncirrhotic patients suggests that this steroid side effect–sparing drug may be effective; however, the few randomized controlled trials of budesonide have not consistently shown efficacy. Although therapy has been shown to be effective for severe autoimmune hepatitis (AST ≥10 × the upper limit of normal or ≥5 × the upper limit of normal in conjunction with serum globulin greater than or equal to twice normal; bridging necrosis or multilobular necrosis on liver biopsy; presence of symptoms), therapy is not indicated for mild forms of chronic hepatitis, and the efficacy of therapy in mild or asymptomatic autoimmune hepatitis has not been established.

Improvement of fatigue, anorexia, malaise, and jaundice tends to occur within days to several weeks; biochemical improvement occurs over the course of several weeks to months, with a fall in serum bilirubin and globulin levels and an increase in serum albumin. Serum aminotransferase levels usually drop promptly, but improvements in AST and ALT alone do not appear to be reliable markers of recovery in individual patients; histologic improvement, characterized by a decrease in mononuclear infiltration and in hepatocellular necrosis, may be delayed for 6–24 months. Still, if interpreted cautiously, aminotransferase levels are valuable indicators of relative disease activity, and, although recommended, many authorities do *not* advocate for serial liver biopsies to assess therapeutic success or to guide decisions to alter or stop therapy. Rapidity of response is more common in older patients (≥69 years) and those with HLA *DBR1*04*; although rapid responders may progress less slowly to cirrhosis and liver transplantation, they are no less likely than slower responders to relapse after therapy. Therapy should continue for at least 12–18 months. After tapering and cessation of therapy, the likelihood of relapse is at least 50%, even if posttreatment histology has improved to show mild chronic hepatitis, and the majority of patients require therapy at maintenance doses indefinitely. Continuing azathioprine alone (2 mg/kg body weight daily) after cessation of prednisone therapy has been shown to reduce the frequency of relapse. Long-term maintenance with low-dose prednisone (≤10 mg daily) has also been shown to keep autoimmune hepatitis in check without the theoretical risk of azathioprine marrow suppression and, in young women of child-bearing age, teratogenicity; however, maintenance azathioprine is more effective in preserving remission.

In medically refractory cases, an attempt should be made to intensify treatment with high-dose glucocorticoid monotherapy (60 mg daily) or combination glucocorticoid (30 mg daily) plus high-dose azathioprine (150 mg daily) therapy. After a month, doses of prednisone can be reduced by 10 mg a month, and doses of azathioprine can be reduced by 50 mg a month toward ultimate, conventional maintenance doses. Patients refractory to this regimen may be treated with cyclosporine, tacrolimus, or mycophenolate mofetil. Similarly, in exploratory studies, infusions of monoclonal antibodies directed at tumor necrosis factor (infliximab) and against the B-lymphocyte antigen CD20 (rituximab) have been reported to be of clinical benefit (improved aminotransferase levels, immunoglobulin G levels, histologic inflammatory activity) as rescue therapy for refractory autoimmune hepatitis. To date, however, only limited, often anecdotal, data in small numbers of patients support these alternative approaches. If medical therapy fails, or when chronic hepatitis progresses to cirrhosis and is associated with life-threatening complications of liver decompensation, liver transplantation is the only recourse **(Chap. 338)**; in patients with severe autoimmune hepatitis, failure of the bilirubin to improve after 2 weeks of therapy should prompt early consideration of the patient for liver transplantation. Recurrence of autoimmune hepatitis in the new liver occurs rarely in most experiences but in as many as 35–40% of cases in others; nonetheless, 5-year patient and graft survival exceed 80%.

Like all patients with chronic liver disease, patients with autoimmune hepatitis should be vaccinated against hepatitis A and B, ideally before immunosuppressive therapy is begun, if practical. Patients with autoimmune hepatitis and cirrhosis should be screened for HCC with ultrasound at 6-month intervals and for gastroesophageal varices with upper gastrointestinal endoscopy at intervals of 1–3 years, based on severity of liver disease.

FURTHER READING

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TABLE 335-1 Risk Factors for Alcoholic Liver Disease

RISK FACTOR	COMMENT
Quantity	In men, 40–80 g/d of ethanol produces fatty liver; 160 g/d for 10–20 years causes hepatitis or cirrhosis. Only 15% of alcoholics develop alcoholic liver disease.
Gender	Women exhibit increased susceptibility to alcoholic liver disease at amounts >20 g/d; two drinks per day is probably safe.
Hepatitis C	HCV infection concurrent with alcoholic liver disease is associated with younger age for severity, more advanced histology, and decreased survival.
Genetics	Patatin-like phospholipase domain-containing protein 3 (PNPLA3) has been associated with alcoholic cirrhosis.
Fatty liver	Alcohol injury does not require malnutrition, but obesity and nonalcoholic fatty liver are risk factors. Patients should receive vigorous attention to nutritional support.

335 Alcoholic Liver Disease

Mark E. Mailliard, Michael F. Sorrell

Chronic and excessive alcohol ingestion is a major cause of liver disease and is responsible for nearly 50% of the mortality from all cirrhosis. The pathology of alcoholic liver disease consists of three major lesions, with the progressive injury rarely existing in a pure form: (1) fatty liver, (2) alcoholic hepatitis, and (3) cirrhosis. Fatty liver is present in >90% of daily as well as binge drinkers. A much smaller percentage of heavy drinkers will progress to alcoholic hepatitis, thought to be a precursor to cirrhosis. The prognosis of severe alcoholic liver disease is dismal; the mortality of patients with alcoholic hepatitis concurrent with cirrhosis is nearly 60% at 4 years. Although alcohol is considered a direct hepatotoxin, only between 10 and 20% of alcoholics will develop alcoholic hepatitis. The explanation for this apparent paradox is unclear but involves the complex interaction of facilitating factors such as drinking patterns, diet, obesity, and gender. There are no diagnostic tools that can predict individual susceptibility to alcoholic liver disease.

GLOBAL CONSIDERATIONS

Alcohol is the world's third largest risk factor for disease burden. The harmful use of alcohol results in about 3.5 million deaths worldwide each year. Most of the mortality attributed to alcohol is secondary to cirrhosis. Mortality from cirrhosis is directly related to alcohol consumption, with the Eastern European countries the most significantly burdened. Cirrhosis and its complications are closely correlated with volume of alcohol consumed per capita population and are regardless of gender.

ETIOLOGY AND PATHOGENESIS

Quantity and duration of alcohol intake are the most important risk factors involved in the development of alcoholic liver disease **(Table 335-1)**. The roles of beverage type(s), i.e., wine, beer, or spirits, and pattern of drinking (daily versus binge drinking) are less clear. Progress beyond the fatty liver stage seems to require additional risk factors that remain incompletely defined. Although there are genetic predispositions for alcoholism **(Chap. 445)**, gender is a strong determinant for alcoholic liver disease. Women are more susceptible to alcoholic liver injury when compared to men. They develop advanced liver disease with substantially less alcohol intake. In general, the time it takes to develop liver disease is directly related to the amount of alcohol consumed. It is useful in estimating alcohol consumption to understand that one beer, four ounces of wine, or one ounce of 80% spirits all contain ~12 g of alcohol. The threshold for developing alcoholic liver disease is higher in men (>14 drinks per week), while women are at increased risk for liver injury by consuming >7 drinks per week. Gender-dependent differences result from poorly understood effects of estrogen, proportion of body fat, and the gastric metabolism of alcohol. Obesity, a high-fat diet, and the protective effect of coffee have been postulated to play a part in the development of the pathogenic process.

Chronic infection with hepatitis C virus (HCV) **(Chap. 334)** is an important comorbidity in the progression of alcoholic liver disease to cirrhosis in chronic drinkers. Even light to moderate alcohol intake of 15–30 g/d increases the risk of cirrhosis and hepatocellular cancer in HCV-infected individuals. Patients with both alcoholic liver injury and HCV infection develop decompensated liver disease at a younger age and have poorer overall survival. Increased liver iron stores and, rarely, porphyria cutanea tarda can occur as a consequence of the overlapping injurious processes secondary to alcohol and HCV infection.

The pathogenesis of alcoholic liver injury is unclear. The present conceptual foundation is that alcohol acts as a direct hepatotoxin and that malnutrition does not have a major role. Ingestion of alcohol initiates an inflammatory cascade by its metabolism, resulting in a variety of metabolic responses. Steatosis from lipogenesis, fatty acid synthesis, and depression of fatty acid oxidation appears secondary to effects on sterol regulatory transcription factor and peroxisome proliferator-activated receptor α (PPAR-α). Intestinal-derived endotoxin initiates a pathogenic process through toll-like receptor 4 and tumor necrosis factor α (TNF-α) that facilitates hepatocyte apoptosis and necrosis. The cell injury and endotoxin release initiated by ethanol and its metabolites also activate innate and adaptive immunity pathways releasing proinflammatory cytokines (e.g., TNF-α), chemokines, and proliferation of T and B cells. The effect of chronic ethanol ingestion on intestinal permeability influences liposaccharide hepatic influx as well as microbiome dysbiosis, further contributing to the pathogenic process. The production of toxic protein-aldehyde adducts, generation of reducing equivalents, and oxidative stress also play a role. Hepatocyte injury and impaired regeneration following chronic alcohol ingestion are ultimately associated with stellate cell activation and collagen production; key events in fibrogenesis. The resulting fibrosis from continuing alcohol use determines the architectural derangement of the liver and associated pathophysiology.

PATHOLOGY

The liver has a limited repertoire in response to injury. Fatty liver is the initial and most common histologic response to hepatotoxic stimuli, including excessive alcohol ingestion. The accumulation of fat within the perivenular hepatocytes coincides with the location of alcohol dehydrogenase, the major enzyme responsible for alcohol metabolism. Continuing alcohol ingestion results in fat accumulation throughout the entire hepatic lobule. Despite extensive fatty change and distortion of the hepatocytes with macrovesicular fat, the cessation of drinking results in normalization of hepatic architecture and fat content. Alcoholic fatty liver has traditionally been regarded as entirely benign, but similar to the spectrum of nonalcoholic fatty liver disease, the appearance of steatohepatitis and certain