CHRONIC HEPATIC INJURY

Chronic hepatic injury is a relatively common disorder with minimal symptoms, yet with long term risk of significant morbidity and mortality. It is defined pathologically by ongoing hepatic necrosis and inflammation in the liver, often accompanied by fibrosis. It may progress to cirrhosis (15-20% in the case of chronic HCV) and predisposes to hepatocellular carcinoma. Most commonly, it is due to chronic viral infection. In the United States alone, there are an estimated 2.1-2.7 million people chronically infected with HCV. (1) There are also approximately 1-1.25 million chronic carriers of HBV in the United States. While prevalence rates for HCV infection generally are between 0.5 and 5% in other parts of the world, prevalence rates for HBV vary markedly, and in many areas HBV is an endemic infection. The prevalence of endemic HBV is in children declining in many parts of the world due to use of HBV vaccine. Clinical findings and laboratory investigation are often adequate to establish the most likely diagnosis, with a predictive value of 88% for alcoholic hepatitis and 81% for chronic viral hepatitis (before availability of HCV tests) compared to biopsy. (216)

Recommendation

In the absence of liver biopsy showing chronic hepatitis, one of the following clinical definitions should be used to diagnose chronic hepatitis:

Persistence of increased ALT for more than 6 months after an episode of acute hepatitis **OR**

Elevation of ALT (without another explanation) on more than one occasion over a period of 6 months. A shorter time may be appropriate in patients with risk factors for chronic viral hepatitis, genetic causes of hepatic injury, or autoimmune liver injury; or in the presence of clinical signs or symptoms of liver disease. (IIB).

Although the definition of chronic hepatic injury by elevated ALT is widely accepted, 15-50% of individuals with chronic hepatitis C infection have persistently normal ALT. (211) The likelihood of continuously normal ALT decreases with increasing number of measurements; even after three normal ALT values, 11% of those with chronic HCV viremia subsequently developed persistently elevated ALT. (211) ALT often fluctuates between normal and abnormal, particularly in chronic hepatitis C; 60% of patients with multiple ALT measurements have at least occasional normal ALT values. (Dufour DR, unpublished observations) The majority of patients with persistently normal ALT have histologic evidence of chronic hepatitis on biopsy, but, in general, milder inflammation, less fibrosis, and lower rates of progression to cirrhosis than do HCV patients with elevated ALT. (185, 217) Center for Disease Control and Prevention guidelines do not recommend treatment of patients with HCV and persistently normal ALT. (218) While long term studies are needed, it appears that the clinical definition proposed will not miss a significant group of patients who require and benefit from treatment.

It is not always possible to distinguish acute from chronic hepatic injury. Most patients with chronic hepatitis C (the most common form of chronic hepatic injury) have ALT values between 1-4 times the upper reference limit, and 90% have maximum ALT

less than 7 times the upper reference limits, values lower than typically seen in acute hepatitis. In about 5% of cases, however, peak ALT may be over 10 times the upper reference limit, often associated with jaundice, in a pattern similar to that seen in acute hepatic injury. (Dufour DR, unpublished observations) In such cases, it is often necessary to do additional testing to rule out another cause of acute hepatic injury.

Screening

General screening of the population for chronic hepatic injury is not cost effective; testing should be limited to high risk individuals. (218, 219) These include those with a family history of genetic diseases known to affect the liver, as discussed below, or risk factors for chronic viral infection (Table 14). ALT is consistently higher than AST with all causes of chronic hepatic injury except alcohol; AST is normal in a significant number of cases. ALT may be normal in patients with cirrhosis, while AST remains elevated. (100, 220) Total and direct bilirubin and alkaline phosphatase are normal in essentially all patients, and not useful in screening. (216, 221, 222) If an elevated ALT is found on routine testing, this should be confirmed by repeat testing before further evaluation. A minority of individuals with only one elevated ALT is found to have liver disease. (221, 223). Patients with slightly elevated ALT (1-2 times the upper reference limit) are more likely to have transient elevation not due to disease; (216, 222, 223) however, about 30% of those with chronic HCV infection have peak ALT less than 2 time the upper reference limit. (Dufour DR, unpublished observations) Since ALT is also found in skeletal muscle, it is advisable to consider history of exercise and, if positive, to consider measurement of creatine kinase to rule out skeletal muscle origin for ALT. (25, 223)

Table 14 – Risk Factors for Chronic Viral Hepatitis (Reference 218)

Established Risk Factors

- Injection drug use
- Chronic hemodialysis
- Blood transfusion or transplantation prior to 1992 (HCV)
- Receipt of blood (including needlestick) from a donor subsequently testing positive for HCV
- Receipt of clotting factor concentrates produced before 1987
- Asian ancestry (HBV)
- Unvaccinated health care workers (HBV)
- Birth to mother with chronic HBV or HCV

Possible Risk Factors

- Body piercing or tattooing
- Multiple sexual partners or sexually transmitted diseases
- Health care workers (HCV)
- Contacts of HCV positive persons

In patients with risk factors for chronic HBV or HCV infection (Table 14), HBsAg and anti-HCV should be measured to screen for chronic infection. Chronic “carriers” of HBV typically have normal ALT (224), and 15-30% of patients with chronic HCV infection have persistently or intermittently normal ALT; however, the likelihood of only normal values falls with frequency of testing. (225) Because 15-20% of individuals with anti-HCV have no detectable viremia, persons with positive anti-HCV and normal ALT should have qualitative HCV RNA performed to identify those with

persistent infection. HCV RNA may be transiently present in the early stages of infection. (157) If a patient has persistently elevated ALT, positive anti-HCV, but negative HCV RNA, the test should be repeated.

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Recommendations

Screening for chronic hepatitis is recommended in asymptomatic high risk individuals (IIB, E).

ALT is the most cost-effective screening test for metabolic or drug-induced liver injury; AST should also be measured with history of alcohol abuse (IIB, E).

Specific viral serologies (HBsAg, anti-HCV), in addition to ALT, should be used in individuals at high risk for viral hepatitis (IB).

If necessary, confirmation of chronic HCV infection in an anti-HCV positive individual should be made by HCV RNA tests; if negative and ALT elevated, HCV RNA should be repeated (IIB).

Differential Diagnosis

If the clinical history suggests alcohol abuse and/or AST is greater than ALT (especially if > 2x ALT), the most likely diagnosis is alcoholic hepatitis. Virtually no other form of chronic hepatic injury causes AST to be higher than ALT unless cirrhosis develops. (221, 222) While the majority of cases of chronic hepatic injury is caused by viruses, drugs, or ethanol, a number of other disorders may produce chronic hepatic injury. Additional tests are not needed if initial evaluation is consistent with hepatitis B or C or alcoholic hepatitis. (222, 226) Prescription drugs may cause persistently increased ALT, most commonly with drugs such as sulfonamides, cholesterol lowering agents, and isoniazid. (198) In one study from an area with low prevalence of viral hepatitis, history of prescription drug use was common in those with chronic hepatic injury and no recognizable etiology despite extensive laboratory tetsing. (227) In patients with elevated ALT, negative viral markers, and negative history for drug or alcohol ingestion, workup should consider less common causes of chronic hepatic injury (Table 15).

Recommendations

Initial evaluation should include a detailed drug history along with measurement of HBsAg and anti-HCV. If anti-HCV is positive, chronic infection should be confirmed by qualitative HCV RNA measurement (IIB, E).

With persistently elevated ALT and negative viral markers, workup should include antinuclear antibodies and iron and iron binding capacity (or unsaturated iron binding capacity) (IIIB).

In patients under age 40, ceruloplasmin should also be measured (IIIB).

In patients negative for these markers, α_1-antitrypsin phenotype may be of use (IIIB).

If these tests are negative or inconclusive, diagnostic liver biopsy should be performed (IIIB).

Table 15 – Other Causes of Chronic Elevation of ALT and/or AST

Cause	Key Features	Screening Test	Confirmatory Test
Non-alcoholic steatohepatitis	Most common cause other than viral, alcoholic	None	Biopsy
Hemochromatosis	Autosomal recessive trait; 1:200 among Northern European ancestry	Transferrin saturation > 45%	HFE gene analysis for C282Y mutation
Wilson's Disease	Autosomal recessive trait; 1:30,000 individuals; hemolytic anemia, renal injury	Low ceruloplasmin in 65-95% homozygous, 20% of heterozygotes	Genetic analysis, low serum copper, high urine copper
Autoimmune hepatitis	Up to 18% of non-viral hepatitis, mainly in young women; increased γ-globulins	ANA and ASMA; false positive anti-HCV common	Biopsy
Primary biliary cirrhosis	Middle aged women; usually mainly elevation of alkaline phosphatase; often associated with Sjogren's syndrome	Anti-mitochondrial antibody	Biopsy
Sclerosing cholangitis	Young to middle aged men; usually mainly elevation of alkaline phosphatase; often associated with inflammatory bowel disease	Anti-neutrophil cytoplasmic antibodies; ASMA, ANA may also be positive	Bile duct imaging
Alpha-1-antitrypsin deficiency	Autosomal recessive trait; 1:1000 to 1:2000. Controversial whether it causes chronic liver disease in adults	Alpha-1-antitrypsin phenotyping	

Workup of Patients Without Obvious Cause for Chronic Hepatic injury

Nonalcoholic Steatohepatitis (NASH) - Occurrence of chronic liver disease histologically resembling alcoholic hepatitis (fatty change or steatosis, neutrophilic inflammatory response, and Mallory bodies) in patients without alcohol abuse has been termed NASH. Many individuals with elevated ALT have steatosis without the complete histologic picture of NASH. (227) NASH is the most common cause of chronic hepatic injury other than viruses and alcohol and the most common cause of cryptogenic cirrhosis. (216, 228) Although it occurs most commonly in middle aged women with obesity and/or diabetes, it also occurs in men and in persons without these risk factors. (228) Patients with NASH commonly have abnormal lipid profiles, although normal results do not rule out this disease. It differs from alcoholic hepatitis in having ALT higher than AST (except in those with cirrhosis) (229). Weight loss may cause significant improvement in enzyme results; in one study, a 1% reduction in weight caused an average fall of 8.1% in ALT. (230) There are no clinical features or laboratory tests that definitively establish a diagnosis of NASH; biopsy is the only diagnostic procedure with adequate specificity.

Recommendations

Biopsy is necessary to establish the diagnosis of NASH (IIB).

Hemochromatosis - An autosomal recessive trait, hemochromatosis is the most common inherited genetic defect in persons of northern European ancestry (approximately 1:200-1:300 in the United States). (231) The vast majority of cases are due to one of two point mutations of the HFE gene on chromosome 6. The majority (60-90%) of affected individuals is homozygous for the C282Y (845A) mutation, while a minority has compound heterozygosity for this mutation and the H63D (187G) mutation. (232) Screening involves detection of increased transferrin saturation (saturation = serum iron (Fe) * 100/total iron binding capacity (TIBC)) (233) or low unsaturated iron binding capacity (234). A transferrin saturation cutoff of ≥ 45% or unsaturated iron binding capacity cutoff ≤ 28 μmol/L (155 μg/dL) has a sensitivity of 90-100% for homozygosity for the C282Y mutation; if fasting specimens are used, specificity is 43%. (235, 236) A recent consensus conference recommends that definitive diagnosis be made by genetic analysis. (237) While several recent publications have shown the feasibility of hemochromatosis screening using transferrin saturation, most organizations and researchers do not currently recommend screening because of unresolved issues regarding ability to convince young adults to be tested, specificity and reproducibility of screening tests, and questions about natural history of untreated disease. (237) Screening has been advocated by the College of American Pathologists (238), and has been estimated to save $3.19 per blood donor screened. (239)

Recommendations

Initial evaluation for hemochromatosis should be by fasting serum transferrin saturation or unsaturated iron binding capacity (IIB).

Transferrin saturation ≥ 45% or unsaturated iron binding capacity ≤ 28 μmol/L (155 μg/dL) should be followed by analysis for HFE gene mutations (IIB).

Screening of the population may be beneficial but is not currently recommended pending clarification of screening benefits (IIB, E).

Wilson's Disease - An autosomal recessive disorder, Wilson's disease occurs in in about 1 in 30,000 individuals in Europe and North America. It is caused by a mutation of a gene on chromosome 13 coding for an ATPase needed for copper transport (240), Wilson's disease may present as liver disease, neurologic problems, or with psychiatric symptoms, almost always before age 40. Most patients who present with liver disease do not have neurologic manifestations. (201) The most common diagnostic finding is low plasma ceruloplasmin. Low levels also occur with malnutrition, protein loss, and advanced liver disease, and falsely normal values can occur with pregnancy, estrogen administration, and acute inflammation. (241) Most references report low ceruloplasmin in 95% of homozygotes and 20% of heterozygotes (241). One study found normal ceruloplasmin in 35% of patients with chronic liver disease due to Wilson's disease (confirmed by genetic studies in 80%), but in only 15% of patients with Wilson's without

overt liver involvement. (201) Other expected findings in Wilson's disease include increased serum free copper, decreased total serum copper, increased urine copper excretion, and increased liver copper content. These tests may also provide misleading results in Wilson's disease patients. (201, 242) Multiple tests are frequently needed to establish the diagnosis.

Recommendations

Testing for Wilson's disease with ceruloplasmin is indicated in patients under age 40 with chronic hepatic injury or fatty liver, and negative workup for viral hepatitis, drug-induced liver injury, and hemochromatosis (IIB).

Screening for Wilson's disease in all patients with chronic hepatic injury is not indicated (IIB, E).

Genetic marker testing may be useful in equivocal cases, but testing must be able to detect multiple mutations in the Wilson's disease gene (IIIB).

Autoimmune hepatitis - Autoimmune hepatitis (AIH) is responsible for up to 18% of chronic hepatitis not due to viruses or alcohol. (243) Several variants of AIH have been described (244). Type 1, found primarily in young and middle-aged women, is the most common form; it is associated with high titers of anti-nuclear antibody (ANA) and/or anti-smooth muscle antibody (ASMA). Type 2, found primarily in children, is common in western Europe but rare in the United States; it is associated with antibodies to liver-kidney microsomal antigen (anti-LKM_1), but rarely with positive ANA or ASMA. Many patients with type 2 also have HCV infection. Type 3, found primarily in young women, is associated with systemic autoimmune disease in many cases. Most affected individuals lack ANA, ASMA, or anti-liver-kidney microsomal antibodies, but are positive for antibodies for soluble liver antigen (anti-SLA). Standardized diagnostic criteria and a scoring system have been defined by an international panel. (206) The classic features of the most common type 1 include elevated aminotransferases; minimal or no elevation of alkaline phosphatase; polyclonal hypergammaglobulinemia (at least 1.5 times the upper reference limit); no evidence of viral infection, risk factors for viral infection, or exposure to drugs or alcohol; and positive ANA or ASMA (at least 1:80). (206) Approximately 40% of patients with chronic HCV infection have a positive ANA or ASMA, usually in low titers. (244) False positive anti-HCV has been reported in 60% of patients with AIH using second generation tests and in 20% using third generation assays (245); anti-HCV typically disappears with successful treatment. (246) In equivocal cases, HCV RNA (or recombinant immunoblot assay) can be used to establish the diagnosis. (245)

Recommendations

Autoimmune hepatitis should be suspected in patients with chronic hepatic injury and increased immunoglobulins and absence of viral markers or risk factors for viral hepatitis (IIIB).

The diagnosis of type 1 AIH can be clinically supported by positivity for either anti-nuclear antibodies (ANA) or anti-smooth muscle antibodies (ASMA) in high titers (IIIB).

Primary Biliary Cirrhosis and Primary Sclerosing Cholangitis – Primary biliary cirrhosis (PBC) and primary sclerosing cholangitis (PSC) are autoimmune diseases causing destruction of bile ducts. Although characteristically causing elevation in ALP and GGT, patients with PBC and PSC may have elevations of AST and ALT and be considered to have chronic hepatitis. Primary biliary cirrhosis is associated with destruction of intrahepatic bile ducts; it is often associated with other autoimmune disorders, particularly Sjogren's syndrome (up to 80% of cases). (247) An autoimmune marker, antimitochondrial antibody (AMA), is found in almost all patients with PBC. Although other diseases may be associated with positive AMA, in PBC the antibody is directed against the pyruvate dehydrogenase complex (so-called M2 type of AMA), particularly to dihydrolipoamide acetyltransferase (E2) and E3-binding protein. (248) About 5-10% of patients have features of both PBC and AIH. (249) PBC is often detected in asymptomatic individuals by finding an elevated ALP. AST and ALT are elevated in about half of cases, although values are above 2x the reference limit in 20%. (250) Primary sclerosing cholangitis is associated with damage to both intra- and extrahepatic bile ducts; 70% of cases are associated with inflammatory bowel disease (Crohn's disease or ulcerative colitis). (251) Perinuclear anti-neutrophil cytoplasmic antibodies are found in about 2/3 of cases. (252) In PSC, antibodies are commonly directed against bactericidal/permeability-increasing protein, cathepsin G, and/or lactoferrin. There appears to be no prognostic significance to the different antibody specificities, although patients with cirrhosis more commonly have antibody to multiple antigens and to antigens other than lactoferrin. (253) Anti-smooth muscle and anti-nuclear antibodies are also present in up to 70% of cases. (254)

Recommendations

Primary biliary cirrhosis or primary sclerosing cholangitis should be suspected in patients with chronic elevation of alkaline phosphatase (IIIB).

The diagnosis can be clinically supported by positivity for anti-mitochondrial antibodies (PBC) or anti-neutrophil cytoplasmic antibodies (PSC) in high titers (IIIB).

Alpha-1-antitrypsin (A1AT) Deficiency – Alpha-1-antitrypsin is the most important protease inhibitor; congenital deficiency occurs in approximately 1 in 1000 to 1 in 2000 persons of European ancestry. The gene for A1AT is located on chromosome 14 (255); deficiency is usually due to a single amino acid substitution that alters carbohydrate binding and impairs release from hepatocytes. (256) The most important deficiency involves homozygosity for the Z variant, termed Pi (for protease inhibitor) ZZ. Deficiency is associated with emphysema and neonatal hepatitis (257); chronic hepatic injury with cirrhosis and hepatocellular carcinoma have also been reported. (d132) Almost all Pi ZZ neonates have evidence of liver injury at birth; this usually resolves by

age 12 years. (257) In adults, 50% of Pi Z positive individuals (either homozygotes or heterozygotes) develop cirrhosis and 31% develop hepatocellular carcinoma. (256) There is also an excess of Pi Z heterozygotes among patients referred for liver transplant, particularly among patients with cryptogenic cirrhosis where approximately 25% of patients are Pi Z positive. (258) There is evidence, however, that AIAT deficiency or heterozygosity for PiZ phenotype may not directly cause liver disease, but increase susceptibility to liver damage by other agents, especially viruses. Two controlled studies found the same frequency of Pi Z (either homozygous or heterozygous) in patients with liver disease and controls. (259) In a study of 164 patients with Pi Z, 40% had chronic liver disease; 87% were also positive for HCV antibodies or HBV markers, and only 11% had no other liver disease risk factors. (260) Because A1AT is an acute phase reactant, quantitative levels may be falsely normal with infection or inflammation, and falsely low levels may occur with malnutrition, protein losing states, or end stage liver disease. In one study, quantitative levels were normal in 42% of heterozygous Pi Z patients with liver disease. (261) Testing for A1AT deficiency should use phenotype analysis rather than quantitative plasma concentration. (256)

Recommendations

Testing for alpha-1-antitrypsin deficiency may be of benefit in patients with chronic hepatic injury and no other apparent cause, although the role of A1AT deficiency in liver disease in adults is not clearly defined (IIB).

Testing is especially important in neonates with evidence of hepatic injury (IIB).

Testing for A1AT variants should be performed by determination of phenotype (IIB).

Screening patients with chronic hepatic injury for alpha-1-antitrypsin deficiency is not recommended (IIIB, E).

Other Viruses

Two other viruses have been suggested as possibly involved in the pathogenesis of chronic hepatitis: hepatitis G (HGV) and TT virus (TTV). Both viruses can be transmitted by transfusion, and chronic viremia is present with both. To date, evidence suggests that infection with these viruses is common, but there is no clear proof that they play a role in liver injury. HGV (and the related GBV-C) are members of the flavivirus family, as is HCV. HGV was first isolated from patients following transfusion, although most showed no evidence of liver injury. (262) HGV can also be found commonly in chronic hepatitis (263), but does not appear to be a common cause of cryptogenic chronic liver disease. (264) This may be because HGV RNA is rarely found in the liver in chronically viremic patients. (265) TTV was first identified in patients with post-transfusion hepatitis. (266) TTV DNA is found in 1-7% of blood donors in the United States. (267, 268). Presence of TTV DNA is no more common in persons with acute non-A-E hepatitis than in other causes of acute hepatitis or in control patients. (268, 269).

Recommendations

Testing for HGV or TTV, in other than a research setting, is not recommended (IIIE).

Monitoring

While ALT is the most clinically used laboratory test for monitoring liver injury, there is often considerable fluctuation in enzyme activities over time (particularly in chronic HCV infection) (217, 270). It is important to measure ALT repeatedly in chronic HCV before concluding that ALT is normal (225); 43% of chronically infected individuals have ALT values fluctuating between normal and abnormal, and 16% of those with normal ALT on their first two visits and 11% of those with normal ALT on their first three visits subsequently developed increased ALT. (211) In patients with chronic HBV infection without elevated ALT ("chronic carriers"), approximately 10% will develop increased ALT on follow-up (224); ALT should therefore be measured periodically even if initially normal.

With both chronic HBV and HCV, clearance of viral markers is the most reliable method for detecting resolution of infection. In untreated hepatitis B, a small percentage of patients spontaneously clear viral antigens; in long term studies, loss of HBeAg occurs in 1/3 to 1/2 of patients (208, 270). In those that lose HBeAg, 5-10% will subsequently clear HBsAg over 10 years of follow-up. (224, 271) HBeAg should be rechecked periodically if initially positive. If HBeAg is negative and anti-HBe is positive, this may indicate either the beginning of viral clearance from the body, or integration of HBV DNA into host DNA and loss of ability to form replicating virus. HBsAg and anti-HBs should be measured periodically to look for viral clearance, as HBsAg will remain positive in those with integration of HBV DNA. In treatment of HBV, likelihood of viral clearance is related to baseline ALT levels; those with elevated ALT are more likely to respond than those with initially normal ALT activity. (272) Successful treatment is associated with loss of HBV DNA, HBsAg, and HBeAg. While there is evidence that quantitative HBeAg correlates well with HBV DNA (273), quantitative HBeAg assays are not commercially available. HBeAg may disappear even in patients who show no response to therapy. (274) Moreover, there is an increasing frequency of "pre-core" mutants that cannot produce HBeAg, particularly in endemic areas in Asia and the Mediterranean region. (275) Patients infected with such mutants have anti-HBe, but continue to have circulating HBV DNA. In infection with normal strains, HBV DNA remains detectable longer than does HBsAg in recovery (276) When viral DNA integrates into the host genome, HBsAg is still produced, although HBeAg and HBV DNA are commonly negative in plasma. (277) With lamivudine treatment, however, production of viral nucleic acid through reverse transcriptase is inhibited (277), although viral DNA levels in the hepatocytes are not changed. (278) For these reasons, use of HBV DNA, HBeAg, and HBsAg may all be useful in monitoring patients with chronic HBV, as no single test provides unequivocal evidence of viral clearance.

Most studies have shown that HCV RNA fluctuates over time, but rarely varies by more than 1 log, and in most cases variation is less than 0.5 log. (279) In untreated individuals tested repeatedly over several years, HCV RNA rises by an average of 0.25 log/year. (281) In some series, however, up to a 3 log difference is seen in patients with

elevated ALT when HCV RNA was measured monthly (282); in about 1/3 of chronically infected patients, HCV RNA can fluctuate between a mean of 10^6 copies/mL and undetectable. (283)

Currently, antiviral treatment is recommended for patients with chronic HCV infection who have elevated ALT and more than mild inflammatory changes on biopsy. The most effective therapy currently available is combined ribavirin and interferon. Laboratory tests have been found helpful in predicting response to varying lengths of therapy and in detecting those who do are not responding to treatment and in whom therapy should probably be discontinued. In those treated with combination therapy, both viral load and genotype have been found to identify patients who may respond to 24, rather than 48, weeks of therapy. (284, 285) In a combined analysis of these two studies, five factors were found useful in predicting response. (Table 16) Persons with genotype 2 or 3, along with 3 or 4 other favorable risk factors, can be treated effectively with only 24 weeks of therapy; all other patients do better with 48 weeks of therapy. (286) The best indicator of viral clearance is persistent absence of HCV RNA (determined by qualitative HCV RNA assays). Absent HCV RNA 6 months after completion of treatment is associated with only 10% likelihood of recurrent HCV viremia. (287) Decrease in viral load in the absence of clearance is not reliable evidence of treatment success; however, failure of HCV RNA to decline to less than 400,000 copies/mL by 12 weeks of therapy is associated with 100% likelihood of persistent HCV RNA at end of treatment. (286) An approach to monitoring treatment of patients with HCV by combination therapy is

Table 16 – Favorable and Unfavorable Risk Factors in HCV Treatment with Interferon and Ribavirin (Reference 286)

Favorable Factors

- Genotype 2 or 3
- Viral load < median (3.5 x 10^6 copies/mL)
- Female gender
- Age < 40 years
- No or only portal fibrosis

Unfavorable Factors

- Genotype 1, 4, 5, 6
- Viral load > median
- Male gender
- Age 40 or above
- Septal or more severe fibrosis

MONITORING COMBINED THERAPY

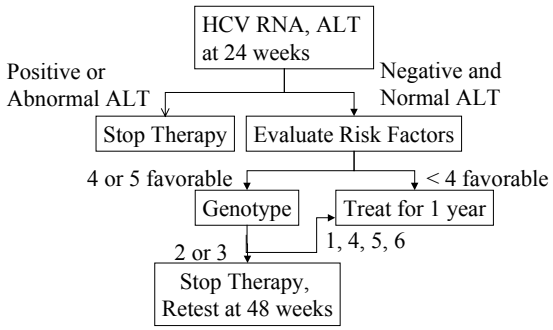

Figure 9 – Approach to Treatment of Hepatitis C – At baseline, HCV RNA (using a quantitative assay linear to at least 4 x 10^6 copies/mL) and genotype should be collected; if facilities do not allow storage at –70° C for at least 6 months, testing should be performed prior to therapy. After six months of treatment, ALT and a sensitive HCV RNA measurement (lower detection limit < 1,000 copies/mL) should be performed. If ALT remains elevated and/or HCV RNA remains detectable, treatment is stopped. In patients showing a response, risk factors (Table 16) are used to determine whether another 6 months of treatment is needed. In patients who are genotype 2 or 3 and who have at least 3 other favorable risk factors, treatment can be stopped.

outlined in Figure 9. Some patients cannot take ribavirin; the only current treatment option for such patients is interferon monotherapy. With this form of treatment, failure of HCV RNA to fall to undetectable or failure of ALT to return to normal at 12 weeks after initiation of therapy is associated with over 95% likelihood of treatment failure, and is considered a reason to discontinue therapy. (288)

The optimal frequency of measurement of laboratory tests in patients with chronic hepatitis C has not been determined. The European Association for the Study of the Liver Consensus Conference on Hepatitis C recommends that complete blood count and liver enzymes be performed every 6 months in untreated patients. (289) The major complications of treatment with interferon are depression, thrombocytopenia and hypothyroidism, while hemolytic anemia is the major complication of ribavirin therapy. The European Association for the Study of the Liver recommends complete blood count weekly during the first four weeks of treatment, and regular determinations after the first four weeks. They also recommend measurement of TSH every 6 months during therapy.

Recommendations

In viral hepatitis, viral markers are the most reliable markers of resolution of hepatitis (IIB).

HCV RNA quantitation and genotype are important determinants of duration of combination therapy. To reduce expenses of testing, if feasible, specimens should be obtained before treatment and stored at -70^{o} C pending results of treatment. If this is not possible, testing should be performed before treatment is begun. (IIB, E)

In patients with HCV treated with interferon and ribavirin, qualitative HCV RNA should be measured after 24 weeks of treatment to determine potential responders. If genotype and quantitative HCV RNA were not performed but specimens were frozen for their analysis before treatment, those with negative HCV RNA and favorable risk factors should have those tests performed. (IB, E)

In patients with HCV treated with interferon monotherapy, qualitative HCV RNA and ALT should be measured after 12 weeks of treatment to determine non-responders. (IIB)

Following treatment in those with negative HCV RNA at 24 weeks, sensitive HCV RNA measurements (currently qualitative assays) should be performed 6 months after the end of treatment to document sustained virologic remission (IIB).

In untreated patients with HBV, HBeAg should be monitored periodically; once negative and anti-HBe is positive, HBsAg should be monitored periodically to determine viral clearance. With anti-viral therapy, HBV DNA should also be used to document viral clearance (IIB).

In treated patients, CBC with platelet count should be measured every week for the first four weeks, then monthly thereafter. TSH should be measured every 3 to 6

months, or sooner if symptoms of thyroid dysfunction develop. Measurement of ALT should be performed at least monthly. (IIIB)

ALT is the best marker of inflammatory activity available, but is of limited utility in predicting degree of inflammation and of no use in estimating severity of fibrosis. (IIB).