

Controversies in Hepatitis C Therapy **CME**

Chairperson: Douglas R. LaBrecque, MD; Faculty: Robert G. Gish, MD; Michael W. Fried, MD; Emmet B. Keeffe, MD

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Introduction

Douglas R. LaBrecque, MD

The first commercial test for the diagnosis of hepatitis C (HCV) was released in 1990. Since that time, our knowledge of the natural history of HCV and the factors that affect progression of the disease has expanded rapidly.

The World Health Organization has recognized HCV as a major public health problem. Over 170 million cases of chronic HCV infection are present throughout the world, with over 4 million chronic carriers in the United States. Therefore, it is imperative that we find a successful treatment for this often-fatal disease.

The growing recognition of the potentially serious consequences of this disease and the availability of steadily improving therapies have led to strong differences of opinion within the medical community. Some of these differences are very basic.

One such controversy is, "Does the patient really need treatment?" Although the identification of the hepatitis C virus and the means by which it is spread have led to a decrease in the incidence of new cases of HCV, the prevalence of the disease will continue to rise for at least the next 15 years. Hepatitis C is already the leading reason for liver transplantation in the United States and Europe. The annual direct and indirect costs attributed to HCV in the United States exceed \$5 billion.

The best currently available therapies can achieve over 60% long-term viral eradication, but only 20% to 30% of patients are believed to be at risk to progress to cirrhosis and its complications. This has led to serious disagreements within the medical community as to the necessity of treating all patients with HCV as opposed to more selective therapy. Dr. Douglas

LaBrecque will present the argument that "virtually all patients should be treated" and Dr. Robert Gish will counter that therapy should be "selective."

Another area where opinions differ is, "Does the patient really need a liver biopsy?" Liver biopsy has always been the "gold standard" in determining the diagnosis and prognosis of liver disease. Recently, however, the great strides made in biochemistry and molecular biology have allowed us to diagnose many liver diseases without the need for a biopsy. Despite this, liver biopsy is still recommended in most cases of HCV prior to initiating therapy because these noninvasive tests are unable to determine the extent and progression of disease. But liver biopsy has certain inherent risks and many patients would prefer to avoid these risks and the possible discomfort associated with liver biopsy.

With the advent of pegylated interferon (PEG IFN) plus ribavirin (RBV) therapy, 80% to 90% of patients with genotypes 2 and 3 can expect to achieve long-term elimination of the hepatitis C virus. This leads many physicians and patients to suggest that this subgroup of patients, as well as those with obvious cirrhosis or risk factors for biopsy, such as hemophilia, do not require a biopsy in order to initiate therapy. Dr. Emmet Keeffe favors this more selective approach to the need for liver biopsy whereas Dr. Michael Fried states, "Liver biopsy -- just do it!"

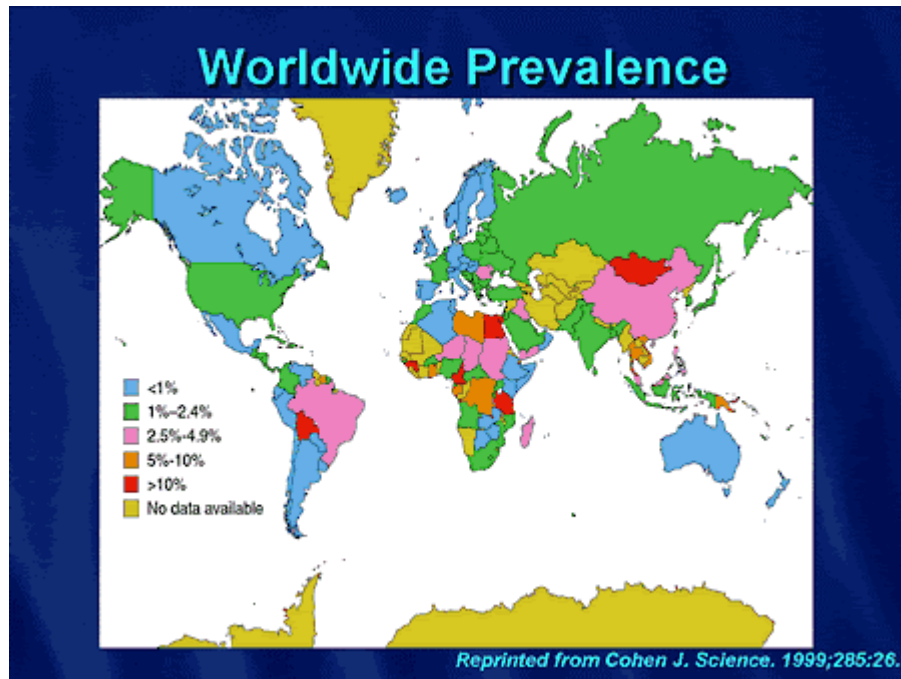
We hope this educational program will challenge you to reevaluate your current thoughts on these controversial issues.

HCV - (Virtually) All Patients Should Be Treated

Douglas R. LaBrecque, MD

Chronic Hepatitis C: Epidemiology and Economic Burden

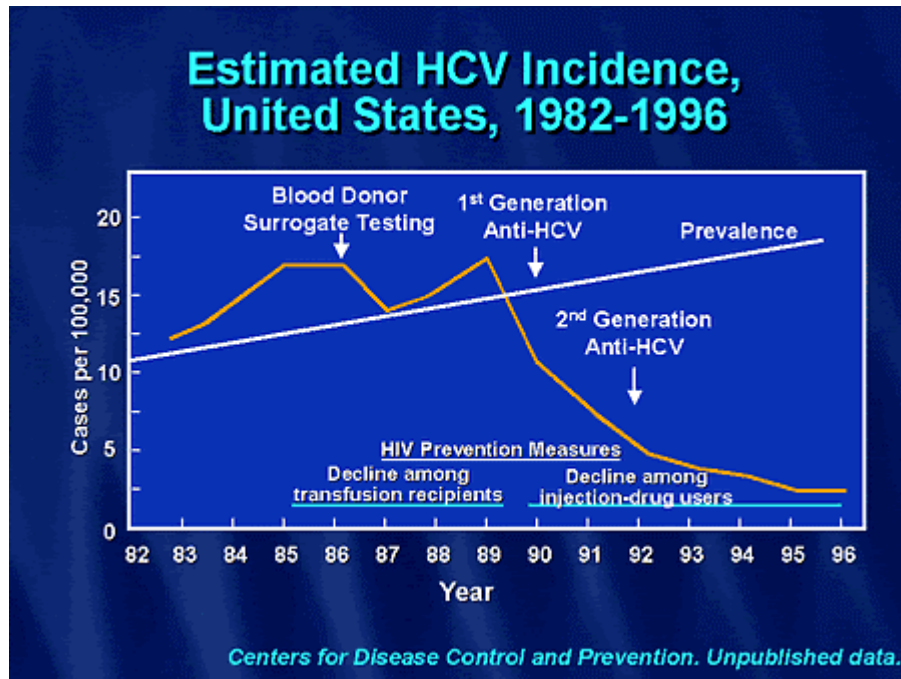
I will be discussing the data which I believe indicate that virtually all hepatitis C (HCV) patients should be treated. Before discussing the controversial aspects of this topic, however, I will discuss the facts, just the facts, about which there is little disagreement.



Slide 1. Worldwide Prevalence

This slide depicts a recent map of the worldwide prevalence of HCV infection. The prevalence of infection is greater than 10% in those areas shown in red, which include areas of Asia, South America, and Africa. Much of the map indicates that between 2.5% and 10% of the population are chronically infected. The Centers for Disease Control (CDC) estimates that 1.8% of the US population is currently infected.

One point eight percent of the US population equates to approximately 4 million US citizens and there are 170 million individuals infected worldwide. Approximately 30,000 new infections occur each year in the United States. Approximately 20% of these individuals will progress to develop cirrhosis over the following 20 years. Eight to 10,000 individuals die each year in the United States from HCV complications. This occurs at a rate of 2% to 5% per year once the patient develops cirrhosis and the risk of developing hepatocellular carcinoma (HCC) is 3% to 7% per year after the development of cirrhosis. Overall, 35% to 40% of all liver transplants performed in the US and Europe are performed for HCV.



Slide 2. Estimated HCV Incidence, United States, 1982-1996

This slide demonstrates that the incidence of acute HCV in the United States fell between 1982 and 1996. During that time there were improved diagnostic tests for HCV and yet the incident rate fell despite our improved ability to diagnose the disease. This was due to a decline in the disease among transfusion recipients and a decline among injection drug users. Because of this there is great hope that there will eventually be a corresponding fall in liver disease related deaths due to this decreased infection rate as well as the development of improved selective treatments.

However, when I add the prevalence of HCV to this graph, you will note that the prevalence has continued to increase despite the decreased infection rate due to the chronic nature of HCV infection and the body's inability to rid itself of the virus on its own. This emphasizes the need for an effective therapy.

Death rates due to HCV are expected to increase over the next 20 years. Estimates of death rates may underestimate the actual death rate because of underreporting of liver disease and underreporting of deaths due to liver disease on death certificates and in other databases (Wong et al. *Am J Public Health.* 2000;190:1562).

Healthcare costs for HCV include managing patients' symptoms, managing other organ involvement, treating HCV with antiviral agents, and managing end-stage liver disease as well as the cost of liver transplantation. Wong and coworkers estimated that the annual US healthcare cost for HCV will exceed \$1 billion by the year 2008 and continue to increase up to at least the year 2015 (Wong et al. *Am J Public Health.* 2000;190:1562).

Leigh and colleagues, using a more inclusive method of estimating costs, arrived at a dramatically higher figure and estimated the yearly cost of HCV in the United States had already exceeded \$5 billion in 1997 (Leigh et al. *Arch Int Med.* 2001;161:2231).

Costs of Medical Care (year)

	Cost in dollars x 10 ⁹
Hepatitis C	5.46
Asthma	5.80
Rheumatoid Arthritis	7.10
Epilepsy	11.10
COPD	23.90
Cancer	107.00

Only HCV mortality is predicted to increase (2-3 fold by 2020)

Leigh et al. Arch Int Med. 2001; 161:2231

Slide 3. Costs of Medical Care (year)

This cost is comparable to what we spend on asthma care in this country and of the diseases listed on this slide, HCV is the only one whose morbidity and mortality are predicted to increase 2- to 3-fold over the next 20 years.

HCV - (Virtually) All Patients Should Be Treated

Douglas R. LaBrecque, MD

Natural History and Risk Factors of Hepatitis C

Progression of Chronic Hepatitis C Studies Having Defined Onset of Disease

Country	Patients (n)	Average Follow-Up (y)	Cirrhosis (%)	Death (%)
Italy ¹	135	7.5	32.3	4.8
Germany ²	86	8.0	24.4	NR
USA ³	39	9.7	20.5	6.0
Sweden ⁴	39	13.0	11.0	2.6
Ireland ⁵	232	17.0	2.4*	NR

*Outbreak related to intravenous gamma globulin.

*15% bridging fibrosis

¹ Tremolada F, et al. *J Hepatol.* 1992; 16:273.

² Hopf U, et al. *J Hepatol.* 1990; 10:69.

³ Di Bisceglie AM, et al. *Hepatology.* 1991; 14:969.

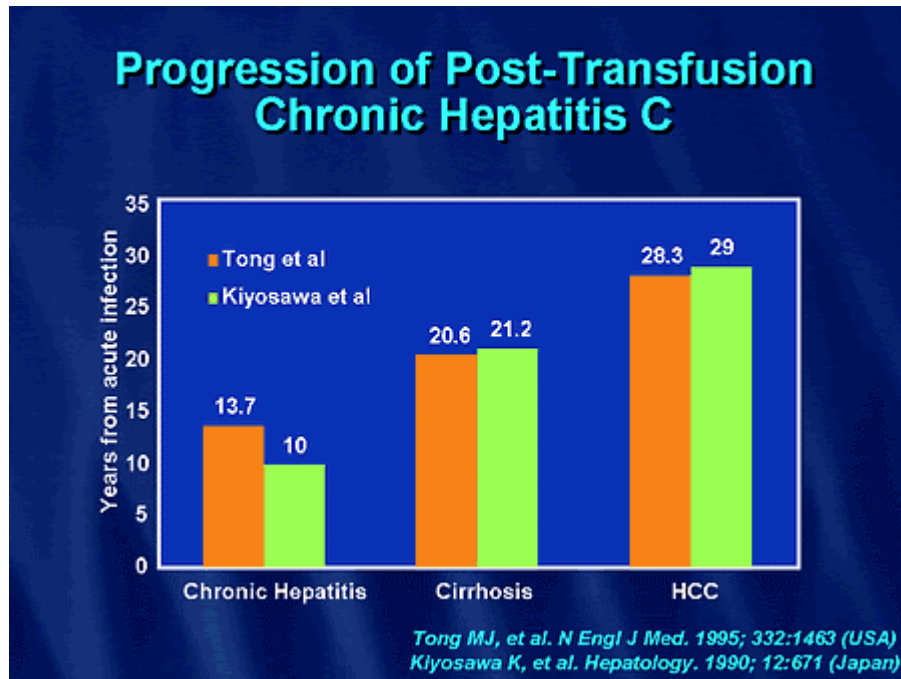
⁴ Mattson L, et al. *Liver.* 1993; 13:274.

⁵ Crowe J, et al. *N Eng J Med.* 1999; 380:1228.

Slide 4. Progression of Chronic Hepatitis C: Studies Having Defined Onset of Disease

A number of studies have defined the natural history of HCV. In general, they reveal a slowly progressive disease leading to cirrhosis in approximately 20% of patients after 20 years. An apparent exception is the Irish Study which reports that only 2.4% of their patients had developed cirrhosis after an average of 17 years follow-up.

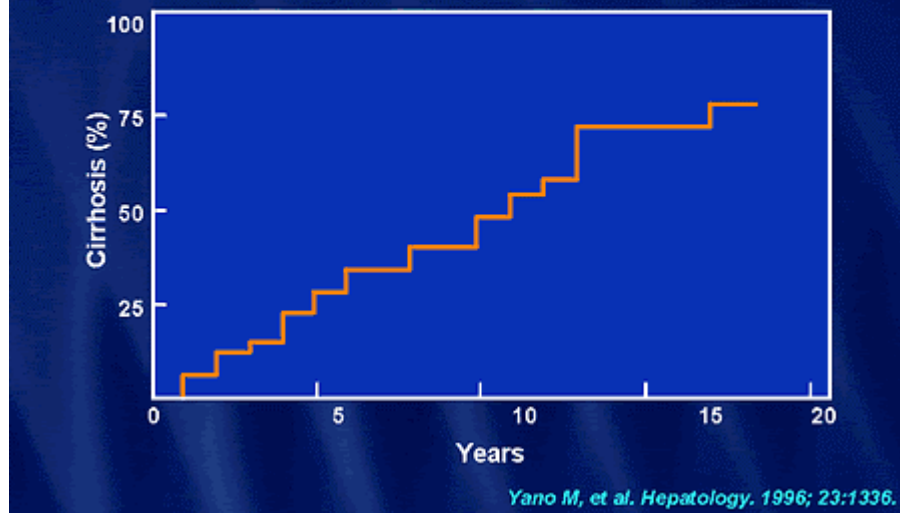
Not often cited when discussing this study, however, is the fact that another 15% had already developed bridging fibrosis, the immediate precursor to cirrhosis.



Slide 5. Progression of Post-Transfusion Chronic Hepatitis C

Two often cited studies, one from the United States and the other from Japan, show remarkably similar rates of progression with chronic HCV appearing after 10 or more years, cirrhosis after 20 years and HCC after 30 years.

Progression of Chronic Hepatitis C



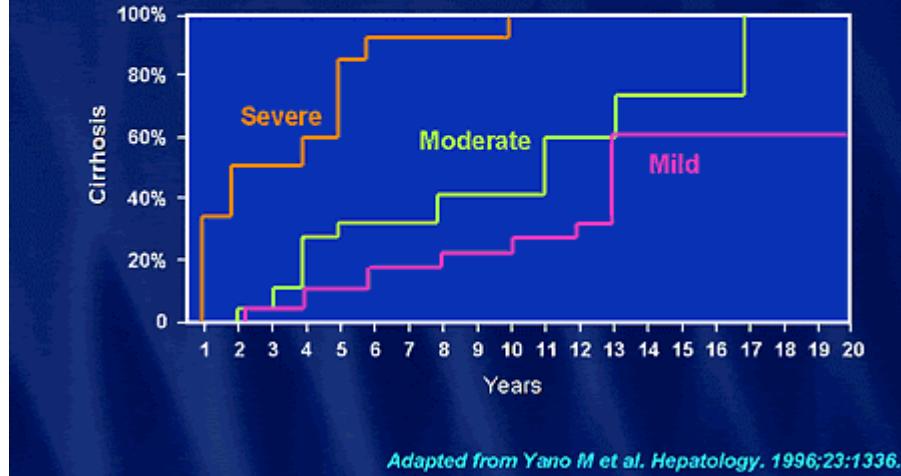
Slide 6. Progression of Chronic Hepatitis C

The report by Yano and colleagues is more typical of the patients we see in our clinics or offices. Often we are unable to determine precisely when the patient acquired HCV. This graph depicts the development of cirrhosis from the time the patient presents to a physician. Within 5 years, 25% are already cirrhotic and almost 50% are cirrhotic by 10 years after presentation, therefore, emphasizing the urgency of treatment.

Fibrosis is the critical transition point in the development of chronic liver disease.

Patients with chronic liver disease of any type generally die from the complications of portal hypertension, variceal hemorrhage, ascites, and hepatic encephalopathy. All of these complications are ultimately the result of fibrogenesis in response to liver damage with the ultimate development of cirrhosis. Thus, preventing progression of fibrosis in the development of cirrhosis is a key factor in the treatment of HCV.

Chronic Hepatitis C: Progression to Cirrhosis According to Baseline Fibrosis



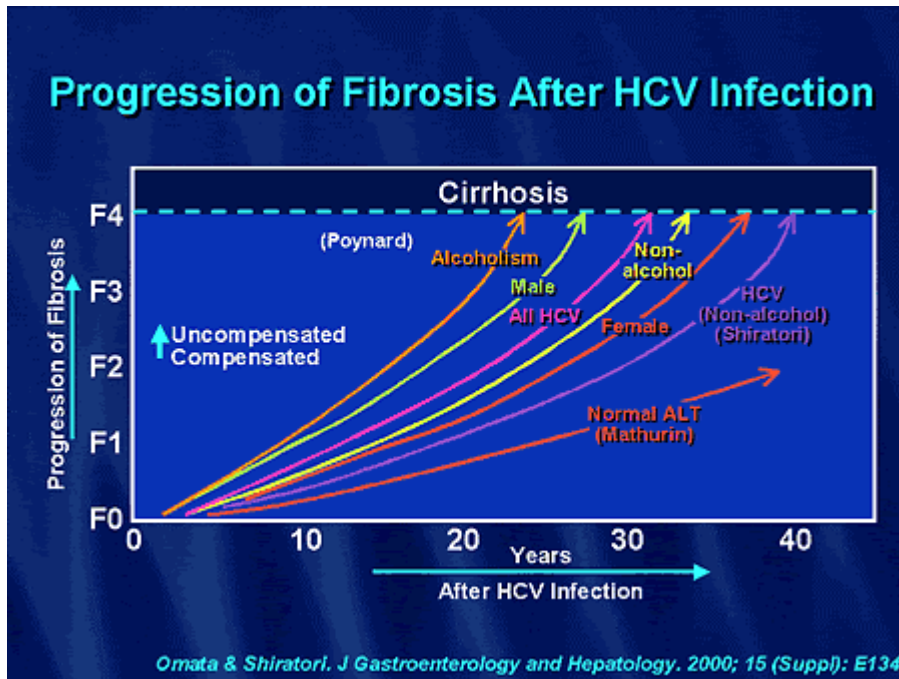
Slide 7. Chronic Hepatitis C: Progression to Cirrhosis According to Baseline Fibrosis

The rate of progression to cirrhosis can be predicted based on the fibrosis present on the baseline biopsy. As demonstrated in this study by Yano, a higher percentage of patients with severe baseline fibrosis (15 of 15 patients in this study) progressed to cirrhosis compared with only 8 of 27 patients initially diagnosed with mild fibrosis. Equally important was the rate of progression. You will note that within 4 years fully 50% of those with severe fibrosis on their initial biopsy were already cirrhotic.

An important question that arises based on these data is do these different clinical characteristics and potential outcomes influence the response to therapy?

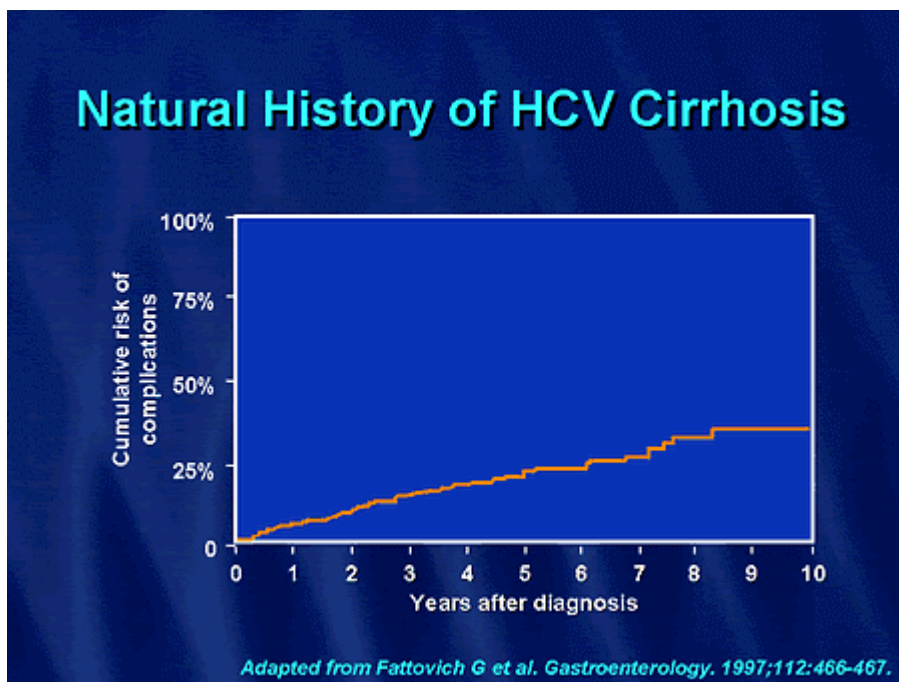
Poynard and others have defined several key risk factors that increase the rate of progression of HCV. A common presentation is a male over age 40 who drinks at least modest amounts of alcohol on a daily basis. Only one of these risk factors is within your or the patient's ability to change. All patients with HCV should be well advised to eliminate all alcohol intake (Poynard et al. *Lancet*. 1997;349:829).

Other factors that have been raised as possible risk factors include obesity and heterozygosity for hemochromatosis. One key point to recognize is that the genotype of the virus has been shown not to be associated with the rate of progression (Poynard et al. *Lancet*. 1997;349:829).



Slide 8. Progression of Fibrosis After HCV Infection

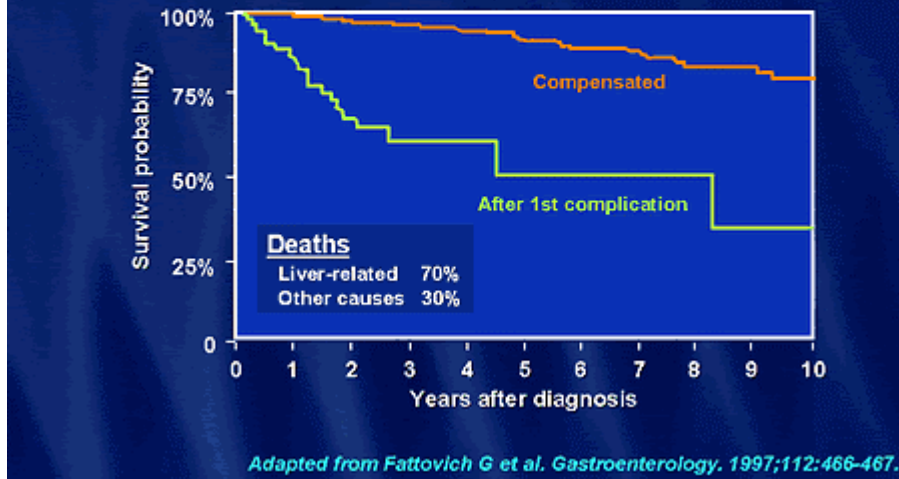
This slide graphically displays the more rapid rate of fibrosis progression in HCV patients with one or more of the risk factors previously discussed. Note, for instance, the rapid rise of the slope labeled alcoholism compared to the one labeled HCV non-alcoholic.



Slide 9. Natural History of HCV Cirrhosis

Even the development of cirrhosis, however, is not necessarily a death sentence. It is important to emphasize to patients that only 25% of patients develop complications 5 years after the diagnosis of cirrhosis as demonstrated in this study by Fattovich and coworkers.

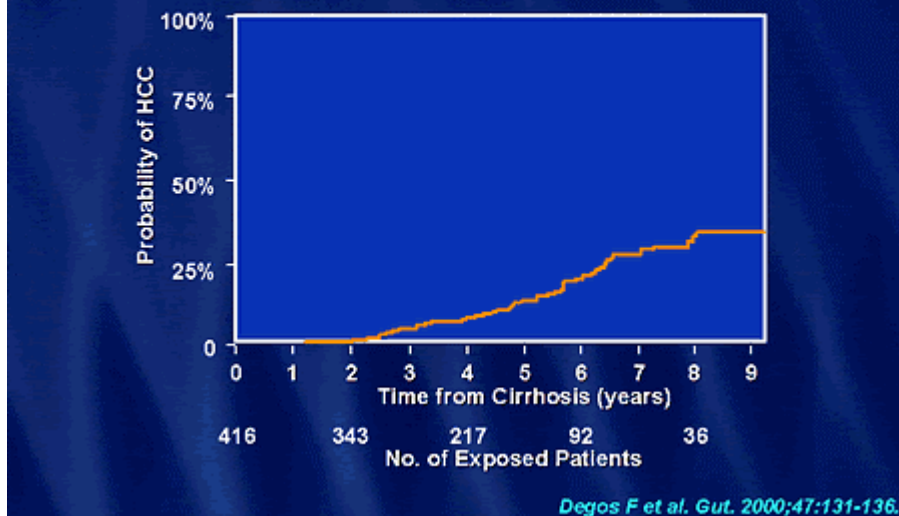
Natural History of HCV Cirrhosis



Slide 10. Natural History of HCV Cirrhosis

HCV-infected cirrhotic patients present a complex set of concerns and potential clinical outcomes. This slide illustrates the probability of survival in 384 patients with HCV-related compensated cirrhosis who participated in a 10-year longitudinal European Study reported by Fattovich and colleagues. During the observation period 13% of the patients died. Seventy percent of these deaths were from liver-related causes, such as HCC, liver failure, and bleeding. The probability of survival was dramatically worse once the first major complication occurred being only 50% at 5 years.

Progression to HCC From Cirrhosis



Slide 11. Progression to HCC From Cirrhosis

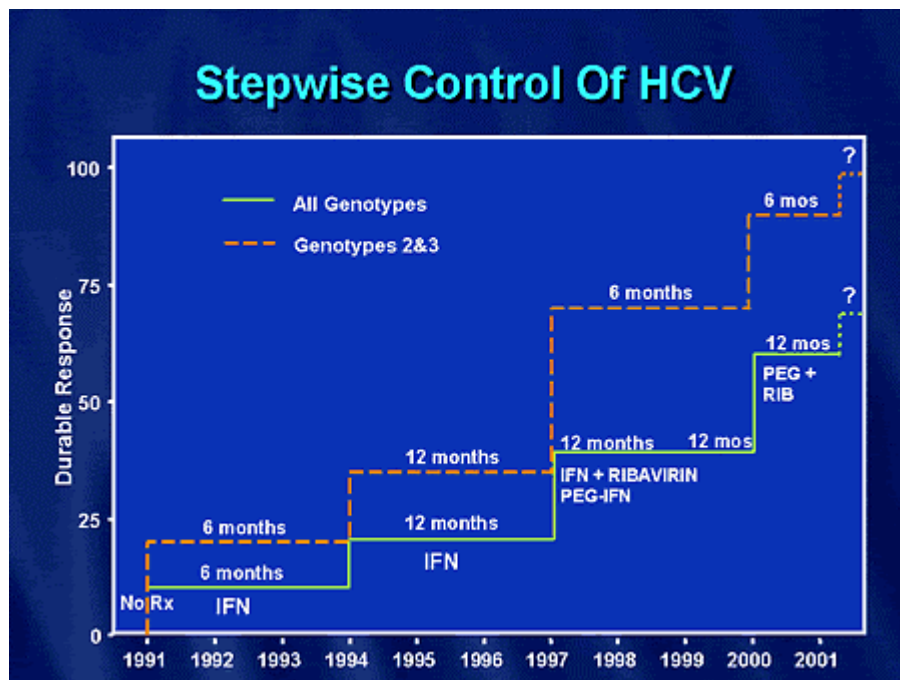
Approximately 20% of patients with cirrhosis will develop liver cancer. This risk is a key reason to consider treatment of patients before they develop advanced fibrosis since the risk of HCC is extremely low in the absence of cirrhosis.

HCV - (Virtually) All Patients Should Be Treated

Douglas R. LaBrecque, MD

Treatment Strategies for Chronic Hepatitis C: Therapeutic Efficacy and Effect on Disease Progression

The goals of therapy for chronic HCV infection can be divided into 2 basic categories. The primary goal is to eradicate the hepatitis C virus. Secondary goals include slowing disease progression, improving hepatic histology, reducing the risk of HCC, and improving health-related quality of life.



Slide 12. Stepwise Control of HCV

As demonstrated on this slide, therapy has improved dramatically over the past 10 years. The green line shows an overall durable response rate that has increased from 10% to 15% with IFN monotherapy to over 50% using pegylated interferon (PEG IFN) plus ribavirin. Response rates are even better in those patients infected with genotypes 2 and 3. As shown in the dashed yellow line, these patients achieved durable response rates of 80% or more.

Peg-interferon Plus Ribavirin Therapy of Chronic Hepatitis C

	SVR	
	Pegasys ^{®1}	Peg-Intron ^{®2}
Overall	56%	54% (61%) ³
Genotype 1	46%	42% (48%) ³
Genotypes 2&3	76%	82% (88%) ³

1. Fried et al. *N Engl J Med* 2002; in press
 2. Manns et al. *Lancet* 2001; 358:958
 3. Weight Based Dosing

Slide 13. Peg-interferon Plus Ribavirin Therapy of Chronic Hepatitis C

This slide reports the overall response (SVR) rates to PEG IFN alpha-2a, also called *Pegasys*, plus ribavirin and PEG IFN alpha-2b, known as *Peg-Intron*, plus ribavirin. You will note that genotypes 2 and 3 have a much higher SVR rate than genotype 1. But even the genotype 1 SVR rate can approach 50%.

Peg-interferon Plus Ribavirin Therapy of Chronic Hepatitis C

	SVR	
	Pegasys ^{®1}	Peg-Intron ^{®2}
Overall	56%	54%
Cirrhotic	43%	44%
Non-cirrhotic	—	57%

1. Fried et al. *N Engl J Med* 2002; in press
 2. Manns et al. *Lancet* 2001; 358:958

Slide 14. Peg-interferon Plus Ribavirin Therapy of Chronic Hepatitis C

Unfortunately, cirrhotics continue to be harder to treat achieving lower SVR rates. Part of this problem may be due to difficulties in tolerating full doses of medication due to low platelet and neutrophil counts.

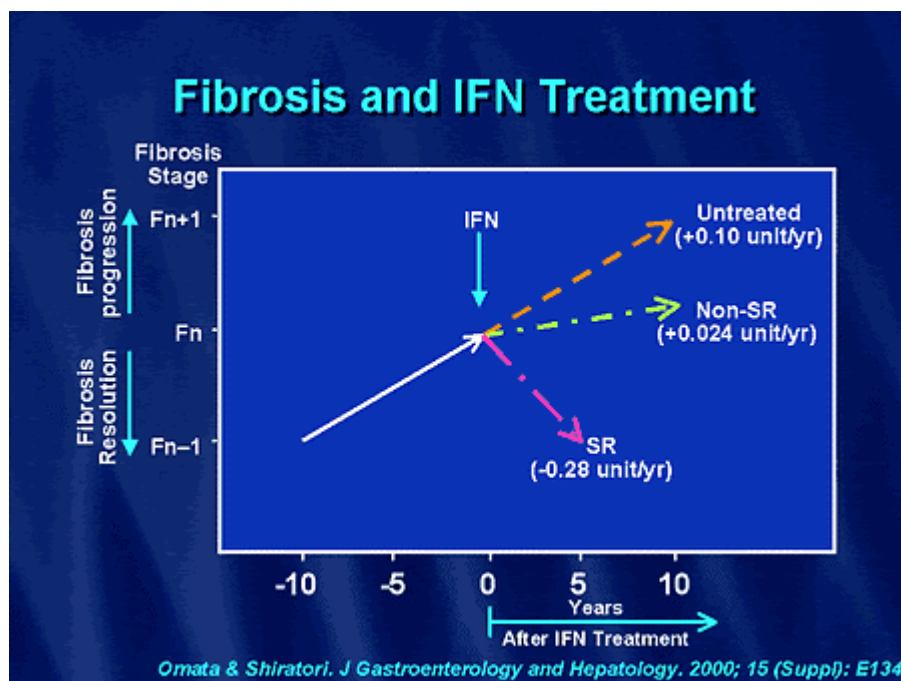
Interferon Effects on Fibrosis

- Decreases rate of progression and may cause regression^{1,2,3,4}
- Reversal of cirrhosis observed⁵
- Most noticeable if SVR^{1,5,6,7}
- Improvement even in nonresponders³

1 Cabellero, T et al, *J Hepatol*, 2001;34:740
2 Brunt, EM et al, *Hepatology*, 2000;31:241
3 Shiffman, ML et al, *Gastroenterology*, 1999 127:875
4 Alric, L et al, *J Hepatol*. 2001; 35:272
5 Poynard, T et al *Hepatology*, 2001;34:244A
6 Bruno, S et al, *J Hepatol*, 2001;34:748
7 Marcellin, P et al, *Ann Intern Med*, 1997; 117:1164

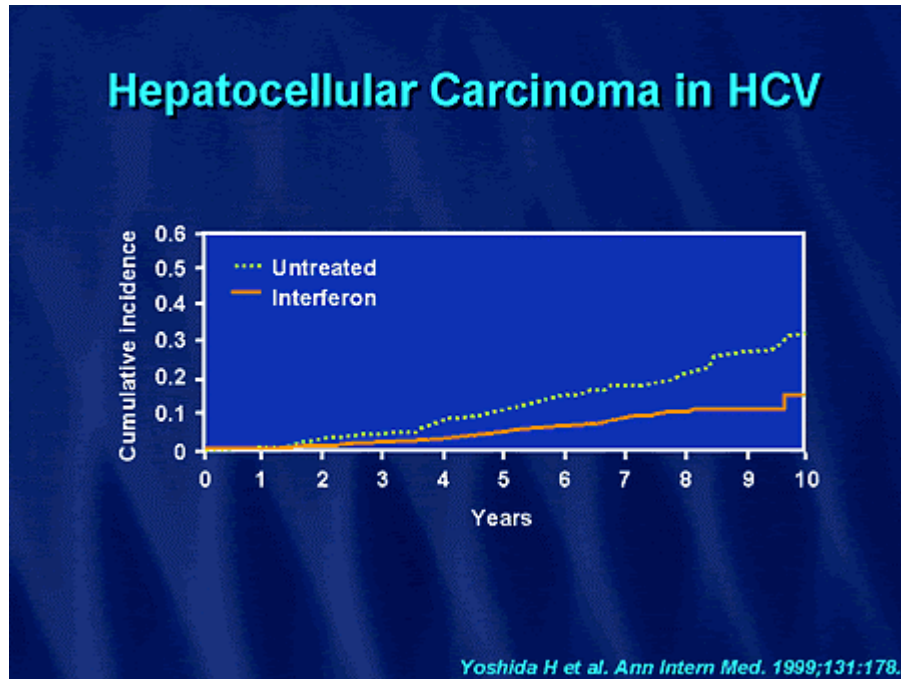
Slide 15. Interferon Effects on Fibrosis

How can IFN help with respect to fibrogenesis? Several studies have examined this question. They have reported decreased rates of progression and even instances of regression with one recent abstract demonstrating reversible cirrhosis in a significant number of patients. This improvement in fibrosis was most noticeable if the patient had a sustained virologic response to treatment. But improvement was noted even in nonresponders. The results of these studies have been promising enough that the National Institutes of Health (NIH) as well as pharmaceutical companies are presently carrying out large trials to determine the potential benefits of long-term therapy with lower maintenance doses of PEG IFN. Recommendations concerning this use of interferon must await the outcome of these trials.



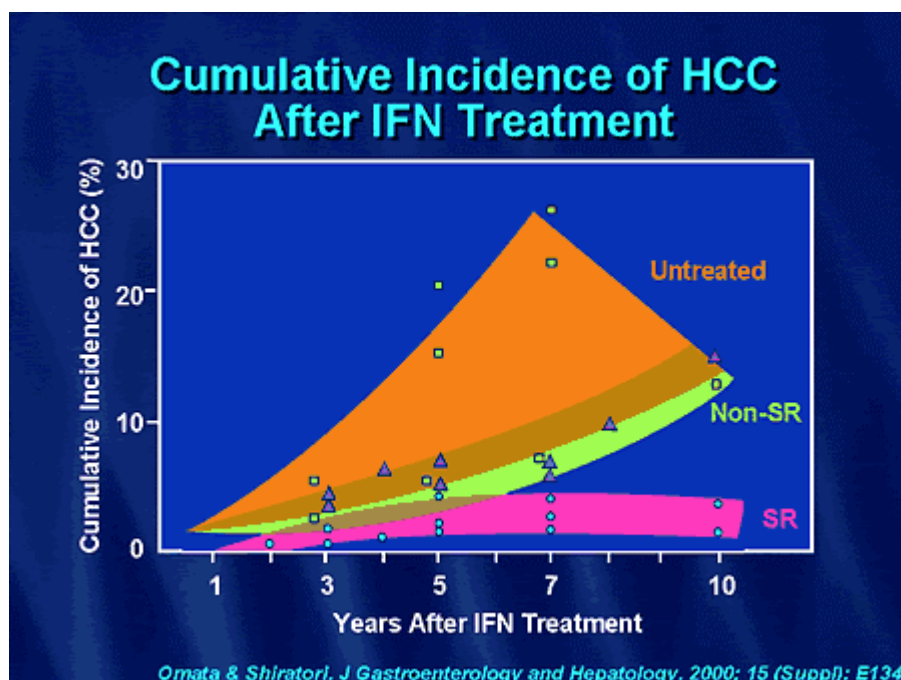
Slide 16. Fibrosis and IFN Treatment

However, extrapolations from the currently available data, such as that by Omata and Shiratori displayed on the current slide, are interesting to review. Fibrosis appears to progress in a linear fashion when followed over time. Sustained responders (SR) to treatment have an actual reduction in fibrosis and even non-sustained responders (Non-SR) appear to have at least a slower rate in the progression of fibrosis.



Slide 17. Hepatocellular Carcinoma in HCV

This graph shows the results of a retrospective cohort study of 2890 patients with chronic HCV carried out in Japan. The study attempted to evaluate the effect of IFN therapy on the incidence of HCC. A number of risk factors were adjusted for including the degree of liver fibrosis. As noted on the slide, IFN therapy significantly reduced the incidence of HCC in these patients compared to patients who remained untreated.



Slide 18. Cumulative Incidence of HCC After IFN Treatment

Omata and Shiratori have summarized several slides in this graph, which shows that SR had the lowest cumulative incidence of HCC but that even Non-SR had a lower incidence of HCC than those who went untreated.

Interferon Therapy and Health Related Quality of Life in Chronic HCV Infection

- Improved HRQL* in patients with SVR to Pegasys^{®1,3,4} and Rebetron^{®2}
- Lasting improvement of HRQL* in cirrhotics with SVR to Pegasys^{®1,3,4}, Rebetron^{®2}, and Roferon-A^{®1}

* Measured using SF-36 instrument

¹Cooksley, et al. *Gastroenterology*. 2001; 120:A382
²Ware, et al. *in review*, 1999
³T. Hassaneln, *Hepatology* 2001; 34: 243A
⁴Bernstein et al. *Hepatology*. 2002; 35: 704-708

Slide 19. Interferon Therapy and Health Related Quality of Life in Chronic HCV Infection

Our final goal of therapy is to improve the health-related quality of life. As seen on this slide, all of the current therapies have been shown to do so when measured using the SF-36 Questionnaire. This improvement appears to be long-lasting even in cirrhotics.

HCV - (Virtually) All Patients Should Be Treated

Douglas R. LaBrecque, MD

Cost-Effectiveness of Hepatitis C Therapy

To this point, I have defined the disease which is serious and I have reported the data supporting therapy with PEG IFN plus ribavirin and the dramatic cost of this disease, over \$5 billion in 1997 alone.

Most infected individuals are now 30- to 49-years-of-age. Gary Davis used a model to project future HCV infection prevalence, disease severity and burden on the healthcare system. The following results were obtained. By the year 2008, the continued maturation of current cases will result in a 61% increase in cirrhosis, a 279% increase in decompensated patients, a 68% increase in HCC, a 528% increase in the need for liver transplantation, and a 223% increase in liver-related deaths. Thus, despite the decreasing incidence of HCV infection, the future

healthcare burden attributable to HCV-related liver disease will be quite significant (Davis GL. *Hepatology*. 1998;28(4 pt 2):390a).

Goals of Therapy

- **Primary goal**
 - Eradicate HCV infection
- **Secondary goals**
 - Slow disease progression
 - Improve histology
 - Reduce risk of hepatocellular carcinoma
 - Improve health-related quality of life

Slide 20. Goals of Therapy

I'd like to review the goals of therapy. Our primary goal is to eradicate the hepatitis C virus. We can now do that in over 50% of patients and in patients with genotypes 2 or 3, we can achieve that in well over 80% of patients. I've also demonstrated that IFN therapy in combination with ribavirin will slow disease progression, improve histology, reduce the risk of HCC and improve health-related quality of life in a significant percentage of patients. Thus, we have a way of achieving all of our goals of therapy in a significant percentage of the patient population.

Cost-Effectiveness of Treatment Comparisons

Treatment or other interventions	Dollars/quality-adjusted life-years gained
IFN monotherapy, 12 mo	\$5,000
Pneumococcal vaccination	\$9,000
Screening mammography	\$20,000
Screening for colorectal cancer	\$86,000
Treatment of hypertension	\$88,000

Bennett WG et al. *Ann Intern Med*. 1997;127:864.
Kim WR et al. *Ann Intern Med*. 1997;127:871.

Slide 21. Cost-Effectiveness of Treatment: Comparisons

If we can agree that ideally all patients with HCV would be better off if the virus could be eliminated from their bodies, the remaining question is how much will it cost?

Dr. Gish will likely raise the question of whether it is worth treating patients with early mild disease. While it is true that many of them will never progress to cirrhosis, they remain at risk of infecting others and we are unable to predict which patients are the ones who will progress to cirrhosis. A watchful waiting approach also requires repeat liver biopsies every 3 to 5 years with their attendant costs, discomfort, and risks (Wong & Koff. *Ann Intern Med.* 2000;133:665).

Drs. Wong and Koff looked at the cost effectiveness of treating such patients. They concluded that histologically mild chronic HCV, initial combination therapy decreased future risk of cirrhosis, prolonged life, and was shown to be cost-effective (Wong & Koff. *Ann Intern Med.* 2000;133:665).

HCV - (Virtually) All Patients Should Be Treated

Douglas R. LaBrecque, MD

Hepatitis C Therapy: Recommendations and Considerations

I have presented the data that define HCV as a serious disease. I have also reviewed the recent studies, which demonstrate a dramatically improved response to therapy for chronic HCV. Based on these data I would strongly recommend therapy for patients with chronic HCV, if their liver biopsy shows significant fibrosis defined as METAVIR stages 2 to 4 or Batts-Ludwig stages 3 and 4. I would also recommend therapy for patients with genotypes 2 or 3 at any stage because of the high degree of response to treatment. Patients with severe symptoms or clinical cryoglobulinemia should also be treated.

Finally, there are certain patients who are very concerned about carrying the virus. They may be worried about transmitting the disease to loved ones. It may be a young woman who is anxious to have a child but wants to eliminate any possibility of transmission to the newborn. Patient concerns must always be listened to carefully and a decision made but if there is no contraindication to therapy, it would be reasonable to treat them on this basis as well (French METAVIR Cooperative Study Group. *Hepatology.* 1994;24:289; Batts KP, Ludwig J. *Am J Surg Pathol.* 1995;19:1409).

In addition, I would recommend therapy be considered for patients even if they have only mild disease. This is based on the information presented earlier demonstrating that milder disease patients have a much higher rate of response to treatment. Additionally, one cannot predict which patients are going to go on to develop cirrhosis. Thus, treating the patient early gives them the best chance of eliminating the virus and avoiding the repeat liver biopsies, which are necessary to follow patients who are not treated.

Compensated cirrhosis is another questionable group. I would recommend treating patients with compensated cirrhosis because a significant percentage of them will still respond to treatment and eliminating the virus will prevent further progression of their disease.

I've also reviewed briefly information suggesting that IFN therapy may actually cause some reversal in fibrosis. This is not an FDA approved indication and would not be enough reason by itself to treat these patients, but could also be taken into consideration with the patient when making a final decision.

I began by saying that virtually all patients should be treated for chronic HCV. Obviously, there are some patients where you may consider deferring or not using therapy at all. Patients who have a long duration of disease with minimal evidence of damage on biopsy, particularly those with genotype 1, may wish to defer treatment until a more effective therapy for genotype 1 is available or one with fewer side effects. Older patients who have minimal disease, particularly those with major medical problems, are also good candidates for deferral of therapy. However, whenever one chooses to defer therapy, follow-up periodic liver biopsies are required and this must be taken into consideration and discussed with the patient as well.

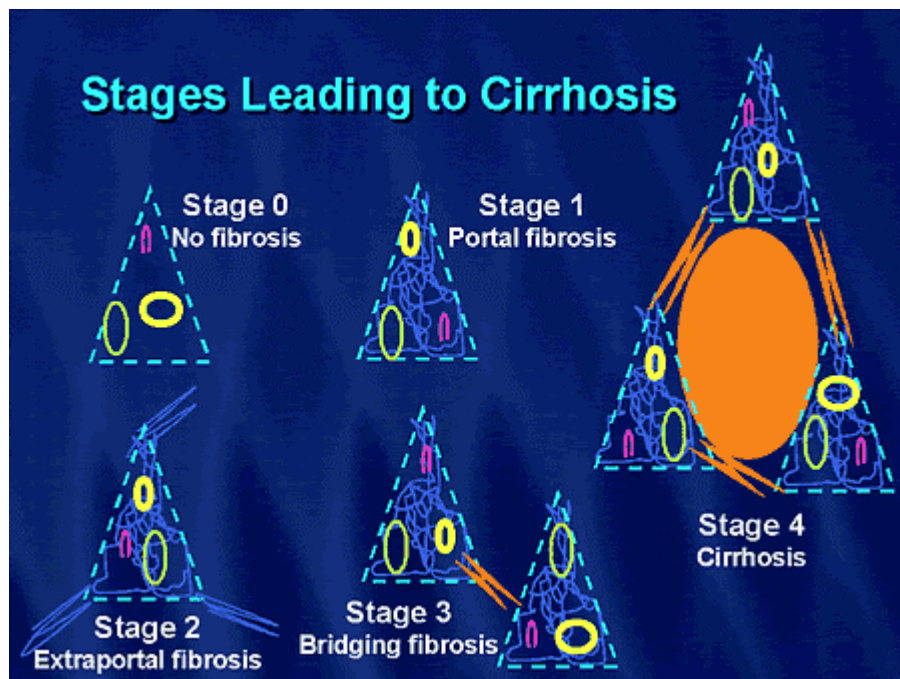
HCV - The Case for Selective Treatment

Robert G. Gish MD

Hepatitis C: Natural History and Independent Predictors of Adverse Outcomes

I will present the case for selective treatment of chronic Hepatitis C (HCV) infection.

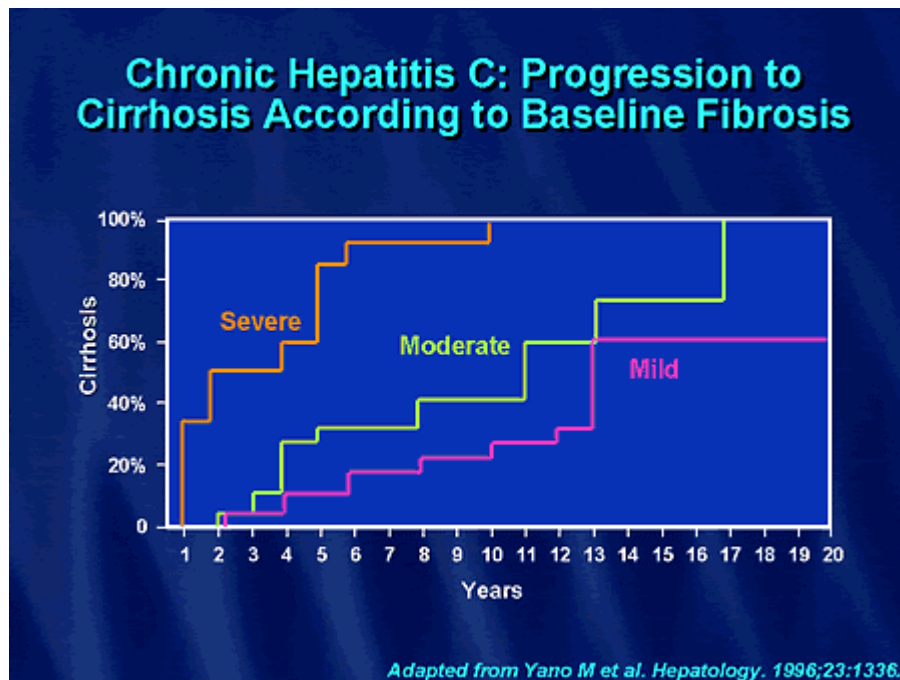
It's important when looking at HCV to realize there are nearly 5 million patients infected with HCV in the United States but only 20% of those patients will develop cirrhosis. Patients at increased risk of developing cirrhosis include patients who are coinfecting with Hepatitis B (HBV) and HIV, patients with alcohol use, organ transplant recipients who are immunosuppressed, and patients with fatty liver. All patients with a positive HCV antibody test need molecular testing for HCV RNA and, if positive, they need to move further through an evaluation process. There is a 3% transmission risk of HCV from vertical, needlestick, and sexual transmission that you also need to communicate to your patients.



Slide 1. Stages Leading to Cirrhosis

I believe the gold standard for evaluating and selecting patients with chronic HCV infection is the liver biopsy. You take the liver biopsy in the context of when they acquired their HCV by

taking a thorough medical history, and risk behavior history, specifically, and then you stage their liver disease by fibrosis score. Patients with Stage 0 and 1 fibrosis very rarely progress to cirrhosis. Patients with stages 2, 3, and 4 with advancing fibrosis are the patients that you want to target and treat in your practice.



Slide 2. Chronic Hepatitis C: Progression to Cirrhosis According to Baseline Fibrosis

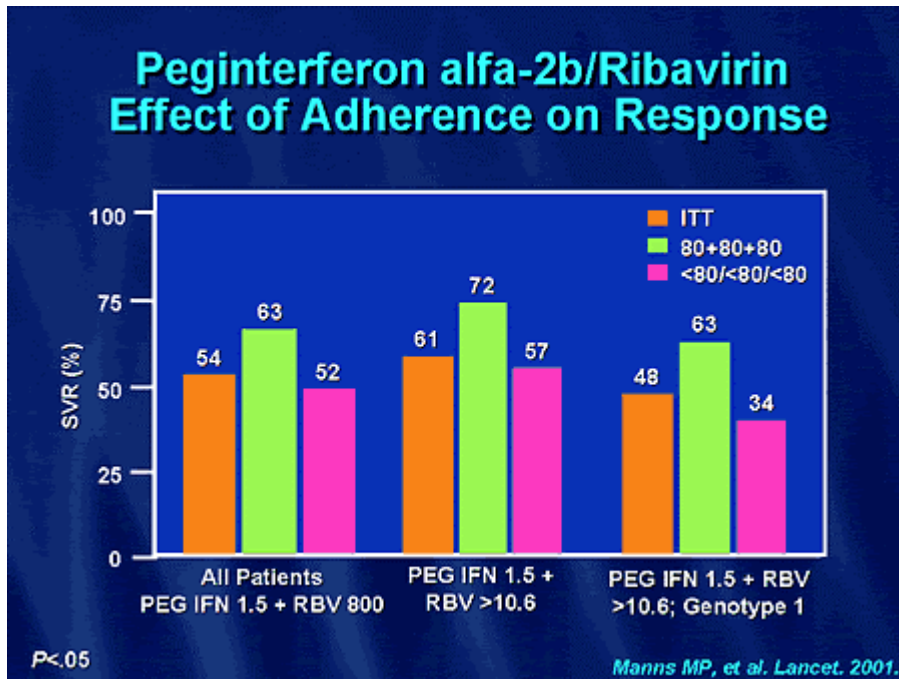
This slide showing severe, moderate, and mild fibrosis from an article by Yano and coworkers in *Hepatology* demonstrating that the level of fibrosis on liver biopsy predicts the timeline to cirrhosis and the percentage chance of developing cirrhosis.

I would like to emphasize that there are independent predictors of adverse outcomes, specifically cirrhosis, in patients with chronic HCV infection specifically, the age of acquiring HCV, alcohol use, obesity, gender, coinfection with HBV or HIV, and immunosuppression, specifically in organ transplant recipients.

HCV - The Case for Selective Treatment

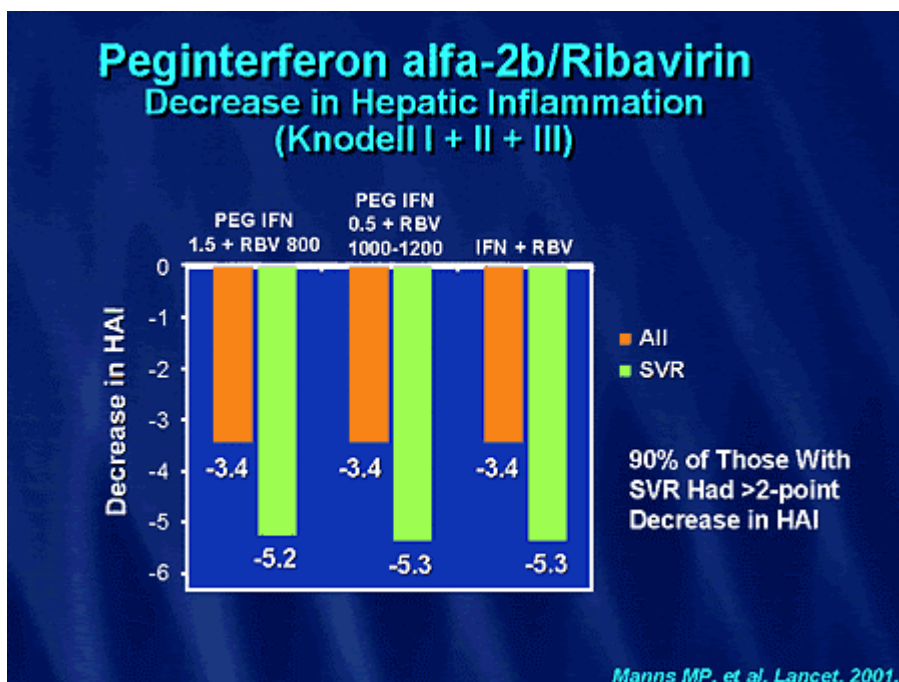
Robert G. Gish MD

Therapeutic Approaches to Hepatitis C: Efficacy and Adverse Events



Slide 3. Peginterferon alfa-2b/Ribavirin: Effect of Adherence on Response

This data from Michael Manns and colleagues in *Lancet* demonstrate that patients with a higher adherence, or in our practice, compliance, have a higher sustained viral response (SVR) rate or cure rate. The 80/80/80 rule means that patients who take more than 80% of their ribavirin (RBV), more than 80% of their interferon (IFN) and more than 80% of the treatment interval recommended have a much higher cure rate. If you think your patient will not be able to adhere or comply, it's best to defer therapy until you can manage that patient better. Specifically, you can manage psychosocial issues, pain issues, irritability, and depression in your practice and then consider starting therapy at some point in the future.



Slide 4. Peginterferon alfa-2b/Ribavirin: Decrease in Hepatic Inflammation (Knodell I + II + III)

This graph demonstrates that patients who have a SVR or cure have a marked reduction in their HAI, which is the Histology Activity Index. But, importantly, if a patient has minimal inflammation how can we improve their biopsy further? I also believe, from my interpretation of the literature, that when you improve hepatic inflammation you can halt fibrosis progression and maybe even reverse fibrosis. But the patient with minimal fibrosis, how can you help them? I think those patients are best deferred until treatment improvements take place in the future.

**Adverse Events:
10% Difference in Incidence
Between Treatment Groups**

	IFN α -2b + RBV (n = 505)	PEG IFN α -2b 1.5 + RBV (n = 511)
Fever	33%	46%
Nausea	33%	43%
Injection-site reactions (all)	36%	58%
Inflammation	18%	25%

Manns MP, et al. Lancet. 2001.

Slide 5. Adverse Events: 10% Difference in Incidence Between Treatment Groups

This table demonstrates adverse events in patients taking IFN and RBV as well as pegylated interferon (PEG IFN) and RBV. It's very important to motivate your patients to move through and complete therapy by treating and managing their side effect profiles. I believe that a liver biopsy showing advancing liver disease will motivate your patient to contact your office, work with your staff and your practice to treat their side effects and maintain full dose and complete the recommended duration of treatment.

Hematologic Adverse Effects

	IFN α -2b + RBV (n = 505)	PEG IFN α -2b 0.5 + RBV 1000-1200 (n = 514)	PEG IFN α -2b 1.5 + RBV 800 (n = 511)
Hemoglobin			
<10 g/dL	11%	13%	9%
Discontinued for anemia	0.2%	0.6%	0.8%
Neutropenia			
Grade 3	7%	11%	18%
Grade 4	2%	2%	4%
Discontinued for neutropenia	0.2%	0.4%	1%

Manns MP, et al. Lancet. 2001.

Slide 6. Hematologic Adverse Effects

As you know with IFN and RBV, there can be a decrease in the hemoglobin and development of significant anemia, specifically from the ribavirin therapy as well as developing neutropenia from patients being treated with IFN and worse with PEG IFN therapy. Patients with severe anemia and neutropenia before treatment should be deferred for therapy since they may suffer significant complications from this type of medication.

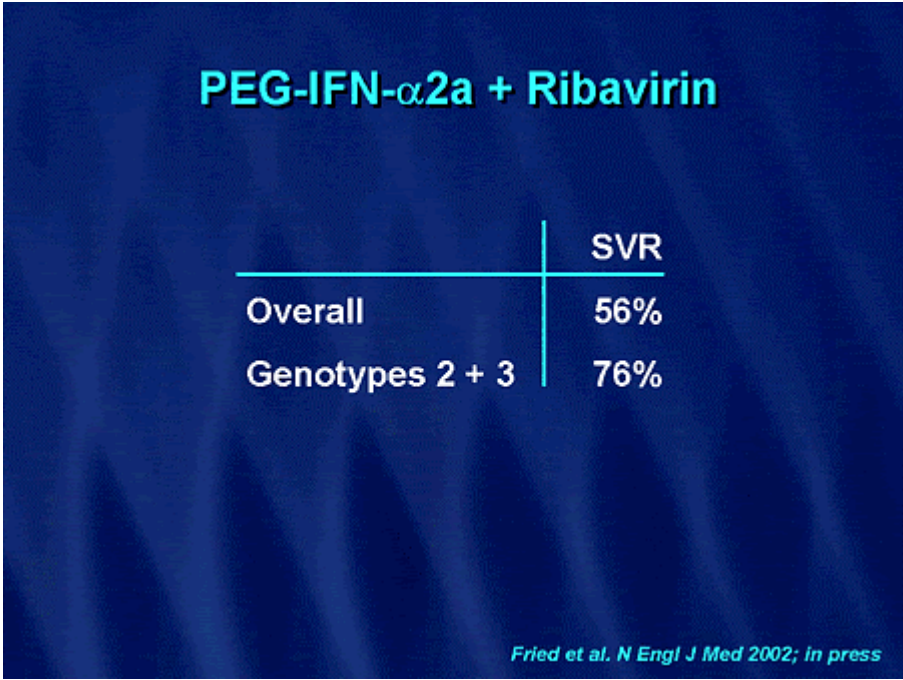
PEG-IFN- α 2a Monotherapy in Cirrhotics

	SVR
Overall	30%
Type 1	12%
Type non-1	51%

Heathcote, E. N Eng J Med 2000; 343:1673

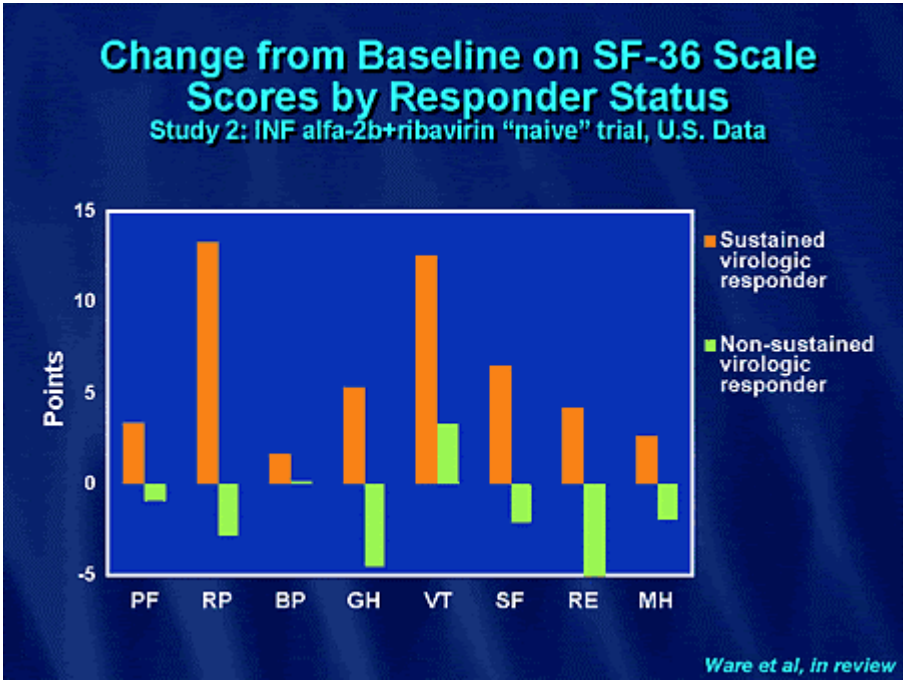
Slide 7. PEG-IFN alfa-2a Monotherapy in Cirrhotics

I would like to emphasize that historically patients with cirrhosis have not responded to IFN monotherapy but now with PEG IFN alfa monotherapy in cirrhotics we have a SVR rate or cure rate of 30%. It's even higher in genotypes 2 and 3 at 51%.



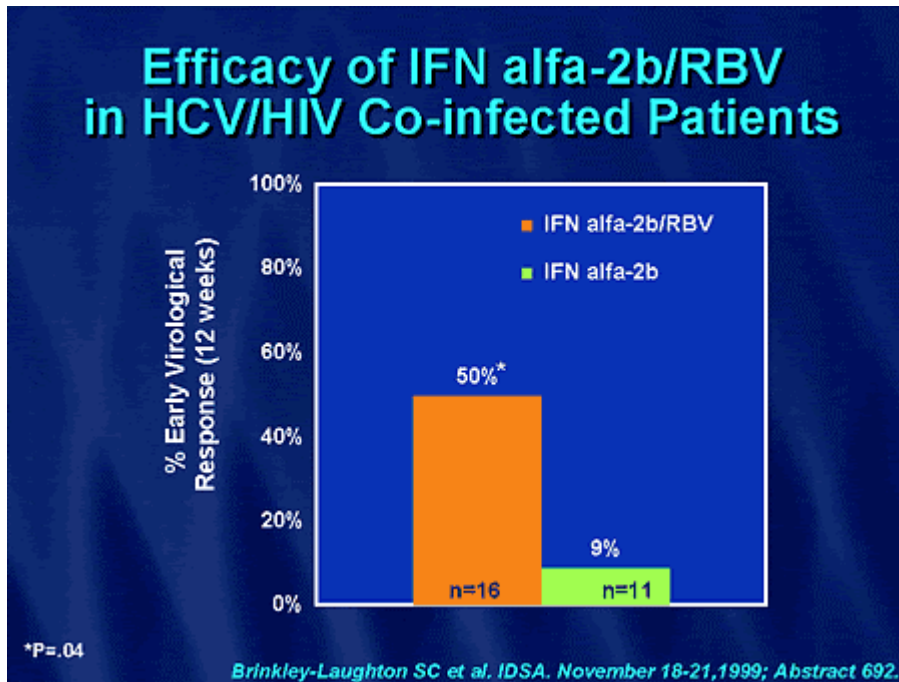
Slide 8. PEG-IFN alfa-2a + Ribavirin

Great advances have now taken place by the addition of PEG IFN alfa and RBV therapy to our armamentarium. Overall, SVR rate or cure rate is now 56% with this combination therapy. It's even more favorable in genotypes 2 and 3 with the SVR rate of 76%.

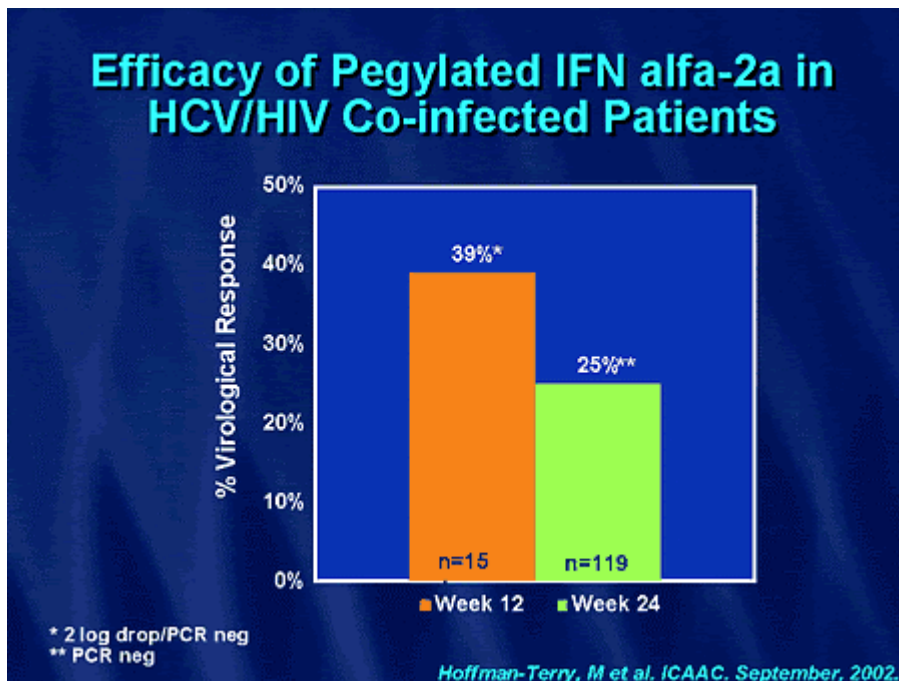


Slide 9. Change from Baseline on SF-36 Scale Scores by Responder Status

This graph demonstrates in patients who are cured or sustained viral responders, that they can have a marked improvement in their quality of life using the SF-36 or Short Form-36 Scale. The bars above the line show an improvement by points in a number of different parameters measured by this test including RP, which is role physical, and VT, which is vitality. Patients who did not have a SVR rate have no change in their quality of life overall.

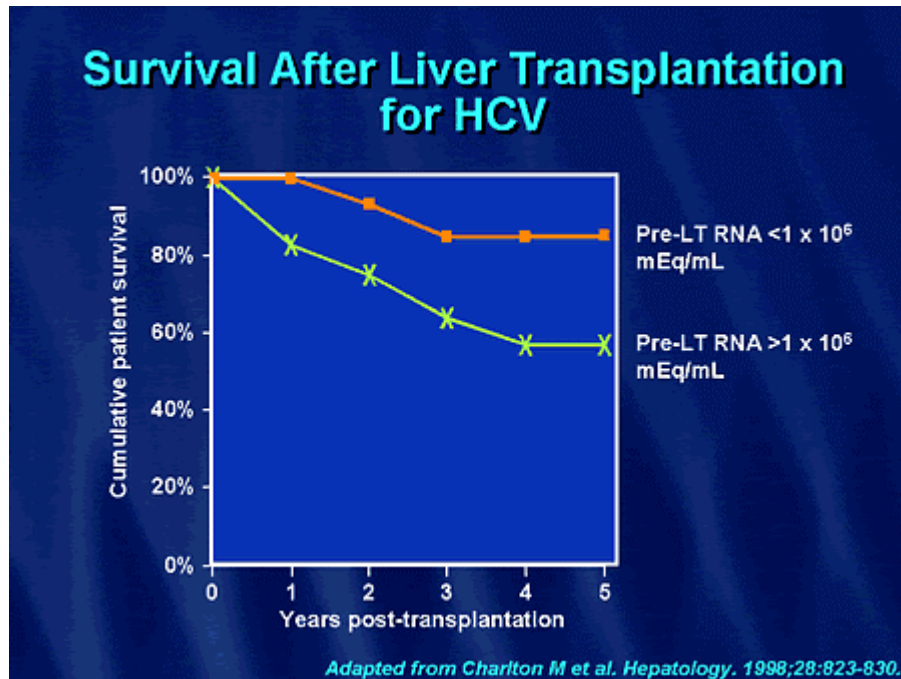


Slide 10. Efficacy of IFN alfa-2b/RBV in HCV/HIV Co-infected Patients



Slide 11. Efficacy of Pegylated IFN alfa-2a in HCV/HIV Co-infected Patients

Historically, IFN alfa therapy for patients coinfecting with HCV and HIV resulted in a nearly zero SVR rate. Now that we have IFN alfa-2b and RBV, and data will emerge for PEG IFN alfa-2b and alfa-2a and RBV for treating these coinfecting patients, I'm expecting a SVR rate to exceed 20% in the near future.



Slide 12. Survival After Liver Transplantation for HCV

In patients who are not immunosuppressed the HCV RNA level in the blood has no correlation to risk of progressive liver disease.

In liver transplant patients, who are immunosuppressed, the pre-transplant HCV RNA level predicts survival or the converse, the chance of dying, long-term. Those patients with a high viral load before liver transplantation, specifically over 1 million copies per mL, are patients who should be targeted for treatment post liver transplantation.. Outcome studies are currently in progress to help demonstrate this point.

HCV - The Case for Selective Treatment

Robert G. Gish MD

Chronic Hepatitis C: Treatment Strategies Under Development

Chronic Hepatitis C: Treatment Strategies Under Development

- **Thymosin- α -1**
 - Sciclone, Thymalfasin, Zadaxin
- **Anti-sense compounds**
 - ISIS
- **Oral interferon inducers**
 - Anadys

Slide 13. Chronic Hepatitis C: Treatment Strategies Under Development

I'd also like to emphasize that, when considering who to treat with HCV, there is great hope for the future with many treatment strategies under development. These strategies include targeting viral replication and enhancing the immune response.

Chronic Hepatitis C: Treatment Strategies Under Development

- **Ribavirin analogue**
 - Roche (ICN), Levovirin
 - no hemolysis
- **Ribavirin prodrug**
 - ICN, Viramidine
- **Polymerase inhibitor**
 - Akros
- **Polyclonal antibodies**
 - Civicir
- **Helicase inhibitors**
 - Schering
- **Protease inhibitors**
 - Vertex
 - Boehringer Ingelheim
- **Small molecules**
 - Lilly
 - SKB
- **E1 E2 polymerization inhibitors**
 - Synergy

Slide 14. Chronic Hepatitis C: Treatment Strategies Under Development

A number of other new products are under development including prodrugs for RBV. We may also have an antibody product that protects people who are exposed to HCV. Molecules that prevent viral replication and release are also under development.

HCV - The Case for Selective Treatment

Robert G. Gish MD

Treatment for Hepatitis C: Indications, Contraindications, and Future Directions

Therapy for chronic HCV infection is strongly indicated for those patients with advanced fibrosis, clinical cryoglobulinemia, severe symptoms, and when there's patient concern about transmission.

Therapy should be considered for patients with a high cure rate or SVR rate, specifically genotypes 2 and 3 and patients with a low viral load.

I want to emphasize that now there are nearly 5 million patients infected with HCV in the United States. There are many new products in development and we can be selective about who we treat. With new single agents or combination therapy, the cure rate will further improve and the treatment interval will shorten.

Liver Biopsy - Just Do It

Michael W. Fried, MD

Liver Biopsy for Hepatitis C: Historical Perspective, Complications, and Cost-Effectiveness

In the management of patients with chronic hepatitis C (HCV), the importance of liver biopsy cannot be overstated. It remains the mainstay of all we do as hepatologists and provides critical information for the management of our patients. In fact, it is of such obvious importance that arguments to the contrary, as will be provided by my esteemed colleague, can only be met with derision apriori.

For obvious reasons, liver biopsy was not widely popular until Dr. Menghini perfected the technique that remains in principle the gold standard for percutaneous liver biopsy. In 1970 Dr. Menghini published an update on the technique that he first introduced in 1958. This is the first suction biopsy and consisted of 14 well-defined steps that he described as the countdown to biopsy. The key to a safe procedure according to Dr. Menghini, was the ritualization of this technique and the rigorous attention to each required element.

Between 1958 and 1970, it was estimated that over 300,000 liver biopsies were performed safely. He reported that the complication rate of his one second biopsy was quite low. The complications were associated with the duration of the intrahepatic phase. In other words, make sure one removes the needle quickly, the size of the needle, and the experience of the operator. As directly quoted from his article, "It is not sufficient to possess a Menghini needle. One must know how to use it." And, "This procedure is not to be undertaken lightly by the uninitiated" (Menghini. *NEJM*. 1970;283:582-585).

Complications of Liver Biopsy

Pain	.056-22%
Hemorrhage	.03-.7%
Bile peritonitis	.03-.22%
Lung biopsy	.001-.014%
Gallbladder biopsy	.034-.117%
Kidney biopsy	.096-.029%
Hemothorax	.18-.49%
Mortality	.0088-.3%

Reddy and Jeffers. Schiff's Diseases of the Liver, 8th ed, 1999

Slide 1. Complications of Liver Biopsy

This technique is associated with little morbidity and mortality. Several studies have looked at the prevalence of complications after liver biopsy. The most common complication is mild pain after the biopsy that can occur in 1 of 5 patients. This is more of a side effect than a complication and is usually easily managed with non-narcotic analgesia. Although different populations around the world have been included, they are in general agreement that the procedure has small risks for serious complications when performed in appropriate patients who did not have obvious contraindications, such as severe coagulopathy or massive ascites.

Opponents of liver biopsy for patients of chronic HCV often cite this study as an argument against liver biopsy. Since Dr. Keeffe is an opponent, he discusses this in more detail. Briefly, the study looked at different diagnostic tests, the utility in guiding the need for therapy, and the cost-effectiveness of each approach for the treatment with interferon (IFN) monotherapy.

What they found was that if level of HCV RNA was used as a discriminant to decide whom to treat, it would miss 36% of potential sustained biological responders. Basing treatment decisions on hepatic histology was more costly and missed 6% of those with sustained response (SR). In this model, subjects with cirrhosis in whom IFN monotherapy was less effective than those with mild disease would have been excluded from therapy.

Their conclusion was that empiric treatment of all eligible patients would be the most cost-effective approach and would not miss any potential sustained virological responders. Liver biopsy did not add anything to the decision analysis and may have slightly decreased life expectancy.

This type of information is very important and I'm sure new analyses are under way using the approved SR rates that are seen with pegylated IFN and ribavirin. However, these types of studies provide information only about one small aspect of the myriad roles of liver biopsy. I submit that regardless of these costs, liver biopsy is still an important tool for the hepatologist (Wong et al. *JAMA*. 1998;280:2088-2093).

Liver Biopsy - Just Do It

Michael W. Fried, MD

Potential Roles of Liver Biopsy in Hepatitis C

This slide shows the potential roles of liver biopsy when we evaluate a patient with chronic HCV. The liver biopsy can be used to confirm the diagnosis, grade and stage the extent of liver injury, provide patients with important prognostic information, and help guide the selection of patients for therapy. All of this information will ultimately provide reassurance to patients that their particular disease state is well understood by themselves and the treating physician. I would like to examine the utility of liver biopsy for providing this information.

In this era of sensitive and specific tests for HCV, I agree that liver biopsy is not required strictly for diagnosis. Clearly, serologic testing for anti-HCV and HCV RNA by sensitive PCR assays is sufficient in order to determine if a patient has chronic HCV. However, there are additional diagnoses that may go undiagnosed on clinical grounds, yet may be identified in liver biopsies. These could have an impact on patient management. So patients could have HCV but also have features of alcoholic liver disease, nonalcoholic fatty liver disease, iron overload, possibly even hemochromatosis, and rarely, alpha-1-antitrypsin deficiency.

The implications of finding alcoholic liver disease are obvious. For nonalcoholic fatty liver disease, however, there is a suggestion that HCV may be associated with greater degrees of fibrosis and may be more difficult to treat.

In addition, in the setting of steatohepatitis residual liver enzyme abnormalities after HCV treatment may be due to steatosis, rather than HCV, a clinical scenario that could be confusing unless the hepatic histology is available.

Finally, hereditary diseases, particularly hemochromatosis or at least unsuspected iron overload could have important implications for counseling, treatment, and monitoring of patients and their families (Ong JP et al. *Liver*. 2001;21:266-271; Adinolfi LE et al. *Hepatology*. 2001;33:1358-1364; Saadeh A et al. *Hepatology*. 2001;33:196-200).

A recent study suggested that additional diagnosis suspected before biopsy could be confirmed by the liver biopsy in patients with an established diagnosis of HCV. Of 47 patients with possible additional diagnoses, 3 patients or 6% had unsuspected nonalcoholic steatohepatitis (NASH) in addition to HCV.

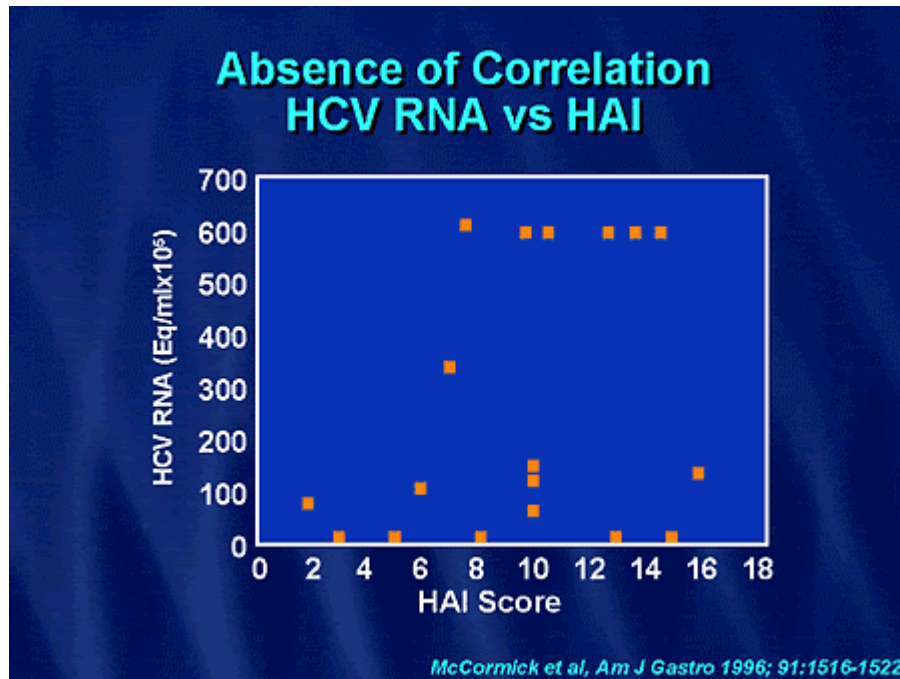
Furthermore, application of a discriminant score to diagnose cirrhosis was not very sensitive in this cohort. The discriminant score utilized the alanine aminotransferase (ALT) to aspartate aminotransferase (AST) ratio (ALT/AST), platelet count, and prothrombin time as surrogate markers for cirrhosis. It missed 20% of those with cirrhosis who were not suspected on clinical grounds (Saadeh A et al. *Hepatology*. 2001;33:196-200).

Grading of liver biopsy refers to the degree of necroinflammatory activity while staging refers to the degree of fibrosis. There is no other way to accurately grade and stage liver disease except by liver biopsy. Biochemical markers, such as ALT, only loosely reflect the grade of necroinflammatory activity seen on liver biopsy and are not at all helpful in predicting the stage of fibrosis.

There has been a flurry of interest in the use of serum markers to predict fibrosis. Among the most studied is hyaluronic acid and procollagen III peptide (procollagen III P). While these serum

tests do correlate to some degree with fibrosis, there is significant overlap in the range of values for individual patients with different stages of disease. It is unlikely that a single test will have the sensitivity or specificity to replace liver biopsy.

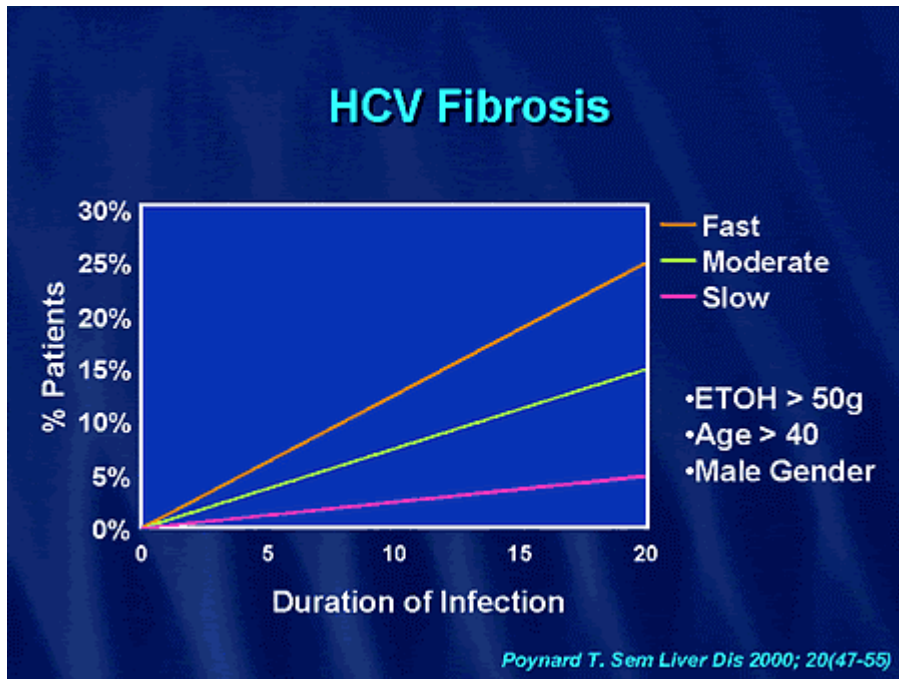
I would like to stress that I am not a liver biopsy fanatic. There are clearly patients for whom a biopsy is unlikely to add additional information concerning the stage of their disease. Thus, patients with HCV and evidence of portal hypertension (HTN) or evidence of hepatic decompensation clearly have underlying cirrhosis. In these situations, the clinical status obviates the need for liver biopsy. But in the absence of stigmata of cirrhosis and portal HTN, liver biopsy is necessary to accurately grade and stage disease activity.



Slide 2. Absence of Correlation: HCV RNA vs HAI

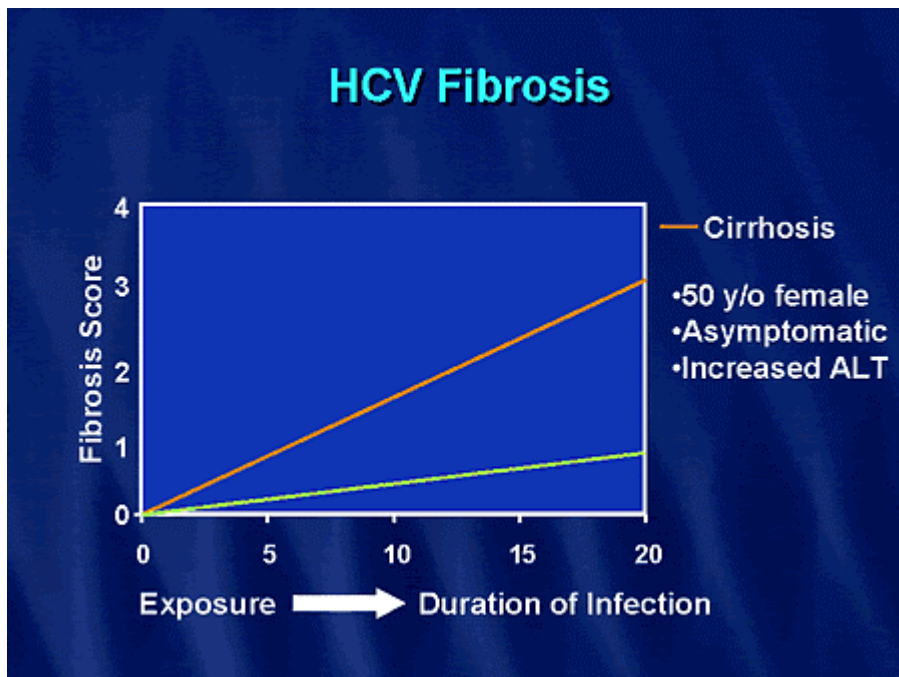
This is an example of the relationship or should I say lack of relationship between the level of HCV RNA and the histologic activity index. Thus, virologic tests are not predictive of the extent of hepatic injury. I think this is an important point about which to educate patients. Very often they become greatly concerned because of meaningless fluctuations in the levels of HCV RNA. These changes are insignificant in terms of HCV disease activity.

Liver biopsy is most useful for determining the prognosis of your patient with chronic HCV. The liver biopsy allows us to correlate the histologic stage with the duration of disease. It can evaluate for compensated cirrhosis that may be clinically silent and in this group, give some idea about the potential for the development of hepatocellular carcinoma (HCC) when advanced fibrosis is present.



Slide 3. HCV Fibrosis

For a given patient evaluating the stage of fibrosis in relationship to the duration of the disease can place into context the likelihood of disease progression in the future. In a study by Poynard and colleagues, subjects could be classified into 3 main groups by the rate at which they developed fibrosis. Certain factors such as excessive alcohol use, older age at infection, and male gender were associated with more rapid fibrosis. However, the degree of fibrosis on a liver biopsy compared with the probable date of infection, and when risk factors are known can also provide some idea of the tempo of fibrogenesis and the risk of future progression.



Slide 4. HCV Fibrosis

As an example, this is how a liver biopsy could affect how we counsel patients about the risk of consequences from HCV based upon their biopsy results. Let's take a 50-year-old woman with asymptomatic HCV who is diagnosed after she went to donate blood. She has mildly elevated liver enzymes. We know she was exposed to HCV about 20 years ago at the time of a blood transfusion during childbirth. Liver biopsy showed stage 1 disease or mild periportal fibrosis. After 20 years of infection, her disease has barely progressed (green line). We should be quite encouraging to this patient when we discuss her long-term prognosis. This may be particularly important if there are relative contraindications to treatment. In certain circumstances, perhaps, the risks of therapy could outweigh the benefits when mild disease is present.

This is the same patient with a different liver biopsy (orange line). Here we see that after 20 years she already has bridging fibrosis. There's a high probability that this patient will develop cirrhosis over the next 5 to 10 years. We may temper our enthusiasm about this patient's prognosis and perhaps be more aggressive in discussions about therapy. Thus, for a given patient a liver biopsy gives us some rational basis to begin our discussion of the natural history in a particular patient.

One intangible benefit of liver biopsy that is difficult to quantify is the role that liver biopsy can play in providing patient reassurance. An informed discussion with the patient about biopsy results in relation to disease duration can alleviate many unfounded fears about imminent death from liver disease. In addition, because of the nonspecific symptoms of HCV, the patient's perception of their disease activity may differ greatly from their actual histologic results. I firmly believe that this information helps tremendously in the management of our patients.

Liver Biopsy - Just Do It

Michael W. Fried, MD

Liver Biopsy in Special Patient Populations

Several groups of patients warrant special mention. While it is believed that patients with persistently normal ALT have milder disease and a better prognosis than those with elevated liver enzymes, those with normal ALT represent the group for whom liver biopsy has been considered controversial. Recently, however, the trend is to biopsy these patients to accurately stage their disease rather than rely on insensitive measures of disease activity, such as ALT. The definition of normal ALT varies from laboratory to laboratory so that abnormal values at one will be within the normal range of another. Is a normal ALT of 55 the same as a normal ALT of 17? Probably not. When biopsies are performed on these patients with normal ALT, the histology is rarely completely normal. Mild to moderate degrees of hepatitis are most common and even cirrhosis can be identified in 3% to 5% of patients with otherwise persistently normal ALT (Marcellin P et al. *Clinics Liver Disease*. 1999;3:843-853).

Patients with hemophilia represent another unique group of patients who have the highest prevalence of HCV infection among any known risk groups. They are all male and were generally infected at a young age. Patients who received clotting factors prior to the improvement in viral inactivation techniques in the mid-1980s were exposed to thousands of potentially infected donors. The prevalence rate of HCV in this population of hemophilic patients is over 90%.

In addition, many patients were also infected with HIV and coinfection has been shown to accelerate disease progression in patients with hemophilia. As therapy for HIV disease improved, chronic liver disease became a major source of morbidity and mortality in these patients.

Earlier it was established that liver biopsy is important for the management of non-hemophilic patients. Therefore, I believe that this group of patients should be managed in accordance with the standard of care, which includes liver biopsy (Fried MW. *Am J Medicine*. 1999;107:85S-90S; Eyster ME. *J AIDS*. 1993;6:602-610).

Of course, concerns about the increased risk of bleeding are appropriate. However, numerous studies have demonstrated that percutaneous liver biopsy can be performed safely in patients with hemophilia by using appropriate factor replacement.

It is crucial to coordinate liver biopsies with the patient's hematologists who could manage their factor replacement. The factor replacement begins immediately before the procedure. Typically, patients who are hospitalized for 24 hours after the biopsy are allowed to continue their own factor replacement at home for a total of 72 hours following the procedure. Protocols for liver biopsies may vary by institution. One caveat is that the presence of inhibitor to factor VIII is a relative contraindication to liver biopsy due to the decreased efficacy of factor replacement. However, the availability of recombinant factor VII, which has been shown to correct clotting abnormalities in patients with hemophilia, may be useful in this group and warrants further investigation.

One cannot ignore the costs associated with performing a liver biopsy in patients with hemophilia. Recombinant clotting factors are expensive and can cost \$3000 to \$7500 depending upon the required amount. In addition, inpatient charges and monitoring fees will add to this burden. One suggested approach has been to perform elective liver biopsies when patients with hemophilia are undergoing other elective procedures that require clotting factor replacement, such as orthopedic surgery and dental work (Fried MW. *Am J Medicine*. 1999;107:85S-90S; Wong VS. *Br J Hematol*. 1997;97:239-240).

Liver Biopsy - Just Do It

Michael W. Fried, MD

Liver Biopsy and Hepatitis C: Summary and Conclusions

In summary, liver biopsy continues to play a major role in the management of patients with chronic HCV. The first NIH Consensus Conference and the European Association for the Study of Liver Diseases (EASLD) both advocated liver biopsy prior to therapy.

Like any diagnostic test, the decision to perform liver biopsy should be individualized for each patient after a discussion about the risks and benefits of the procedure. Patients with stigmata of cirrhosis do not need liver biopsies for the purposes of staging their disease. Liver biopsies should be considered for patients with normal ALT because biochemical parameters do not correlate with disease severity. However, biopsies may influence treatment decisions particularly when there are relative contraindications to therapy.

Most importantly, liver biopsy is absolutely critical for accurate staging, for establishing the prognosis and for counseling patients with HCV. No other tests currently available can duplicate the information obtained from a sliver of liver.

Liver Biopsy - Just Think About It

Emmet B. Keeffe, MD

Liver Biopsy: Indications, Contraindications, and Complications

I'd like to convince you that we should do liver biopsy in many patients but not all patients.

The historical role of liver biopsy was critical in the diagnosis of all patients with acute and chronic liver diseases. However, in our current practices the diagnosis of chronic liver disease is now made by very sophisticated virological, immunological, and genetic testing. For example, we have serologic and virologic tests that diagnose hepatitis A through E, we have antimitochondrial antibody (AMA) that allows the easy diagnosis of primary biliary cirrhosis. We have antinuclear antibody and smooth muscle antibody for autoimmune hepatitis and we have both standard laboratory studies and genetic tests to diagnose all of our genetic liver diseases.

Thus, today in our practice, liver biopsy is reserved primarily for staging and in certain special situations like in allograft dysfunction after transplantation or when we need to analyze a specimen for iron or copper content.

I would now like to review the usual indications for a liver biopsy. Firstly, to evaluate chronically elevated aspartate aminotransferase (AST) or alanine aminotransferase (ALT) levels of uncertain cause; to confirm the diagnosis of chronic liver disease, although as we'll see we can now diagnose most liver diseases without the biopsy based on good biochemical tests; to grade and stage chronic hepatitis, which is the prime indication we use biopsy today; and to determine the etiology of hepatic neoplasms when the imaging studies are equivocal or uncertain.

We need to evaluate the response to treatment in certain circumstances, such as autoimmune hepatitis or when we are doing pharmaceutically funded clinical trials, and we need to look at the outcome of a course of treatment. And then there are special circumstances. We need to evaluate liver transplant allograft dysfunction; to measure iron or copper in certain circumstances; and rarely, to culture for organisms.

There are also less certain indications for liver biopsy. One is to evaluate the cause of acute hepatitis. In acute viral hepatitis the diagnosis is usually obvious based on serologic and virologic tests. However, there are other circumstances, for example, acute hepatitis as a presentation of autoimmune hepatitis that requires a biopsy for confirmation of diagnosis or sometimes in suspected acute drug-induced hepatitis, a liver biopsy may be helpful.

In typical primary biliary cirrhosis (PBC) with an elevated alpha phosphatase and a positive AMA, liver biopsy is less often used than it had in the past. In typical primary sclerosing cholangitis (PSC) with a diagnostic cholangiogram, liver biopsy likewise is less often used. To stage PBC and PSC is less important because therapy is relatively standard and we will know when there's cirrhosis and a need for liver transplantation. And finally, Budd-Chiari syndrome is typically diagnosed by imaging studies and does not usually require a biopsy.

Other less certain indications include a typical hepatocellular carcinoma (HCC) or hepatic metastasis. We do not want to biopsy certain focal lesions, such as a cavernous hemangioma, and I would put forth, although it's a bit controversial, that we probably do not want to biopsy all patients who have nonalcoholic fatty liver disease (NAFLD) particularly if we suspect there's only simple steatosis, and, I do not think we need to biopsy all chronic hepatitis B (HBV) and Hepatitis C (HCV) patients.

I'd like to address the contraindications to liver biopsy starting with the absolute contraindications. We cannot do a liver biopsy if a patient is not cooperative. We must also have satisfactory coagulation and the usual rules for impaired coagulation that make liver biopsy a risk for bleeding such as a prothrombin time (PT) of equal to or more than four seconds over control, or an International Normalized Ratio (INR) equal to or greater than 1.5, a platelet count according to different rules less than 50,000 or less than 60,000, or a bleeding time - although we do not do this routinely any longer - of equal to 10 minutes or more. We don't want to do a biopsy if we presume there's a vascular tumor such as a hemangioma, echinococcal disease, which does not come up very often, or high-grade biliary obstruction from imaging studies.

Relative contraindications to a liver biopsy include ascites, severe chronic lung disease, infections either in the right pleural cavity or below the right diaphragm, amyloidosis, myeloproliferative diseases, and hereditary hemorrhagic telangiectasia. The latter 3 have been reported in some studies to be associated with an increased tendency for bleeding. Thus, these are relative and not absolute contraindications.

I would now like to review the known complications of liver biopsy, which we have to take in context of decisions in our practice regarding performance of biopsy. First of all pain. Pain occurs in .06% to 22% of patients in the literature. Although in my own practice I must say, pain occurs routinely in from 15% to 30% of the patients, and it may be pleuritic, peritoneal, or diaphragmatic. Some patients may have a vasovagal reaction with a faint. Hemorrhage is our most feared complication which occurs in .2% to .3% and bleeding may be in the peritoneal cavity (.03% to .7%), within the liver or in the subcapsular space (.06% to 23%), or within the biliary tree (.06% to .2%). And once in a while, in .001% to .4% of the cases we may biopsy another organ. And the one we particularly fear is the gallbladder although the lung, kidney, and colon may also present problems if they are hit rather than the liver (Reddy and Jeffers. *Schiff's Diseases of the Liver, 8th ed.* 1999).

Other complications include bile peritonitis (.03% to .2%), infectious problems including bacteremia, sepsis (.09%), or abscess, pneumothorax or pleural effusion (.08% to .3%), hemothorax (.2% to .5%), arteriovenous fistula (5.4%), and reactions to the anesthetic agent (.03%) (Reddy and Jeffers. *Schiff's Diseases of the Liver, 8th ed.* 1999).

**Percutaneous Liver Biopsy
Complications – “Bottom Line”**

- **Pain**
– 20-30%
- **Severe complications**
– 0.3% (CI, 0.28 - 0.35)
- **Mortality**
– 0.03% (CI 0.02 – 0.05)

Fattovich et al. Sem Liver Dis 2000;20:47

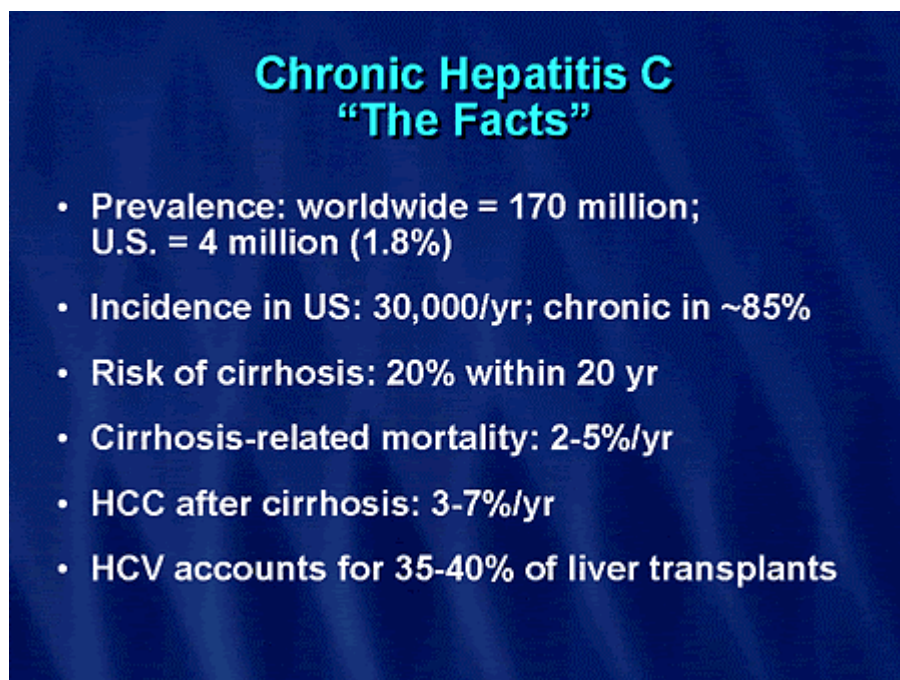
Slide 1. Percutaneous Liver Biopsy Complications -- "Bottom Line"

I've given you a laundry list of all of the complications of liver biopsy. This is now the bottom line. This is what I tell my patients as I approach them before a liver biopsy. You can expect pain in 20% or 30% of biopsies, severe complications occur in 3 per 1000 and the ones that we worry about are hemorrhage or perforation of another organ, and a death rate occurs with a frequency of about 3 per 10,000.

Liver Biopsy - Just Think About It

Emmet B. Keeffe, MD

Chronic Hepatitis C: Epidemiology and Natural History



Chronic Hepatitis C
"The Facts"

- Prevalence: worldwide = 170 million; U.S. = 4 million (1.8%)
- Incidence in US: 30,000/yr; chronic in ~85%
- Risk of cirrhosis: 20% within 20 yr
- Cirrhosis-related mortality: 2-5%/yr
- HCC after cirrhosis: 3-7%/yr
- HCV accounts for 35-40% of liver transplants

Slide 2. Chronic Hepatitis C: "The Facts"

I now want to move to the focus of our point/counterpoint and discuss a little background regarding chronic HCV. The prevalence worldwide is huge, 170 million infected individuals. In the United States 4 million or 1.8% of the adult population. The incidence of new cases has declined to approximately 30,000 cases per year but the infection is chronic in the majority, about 85%. The risk of cirrhosis appears to be at least 20% within 20 years and may approach 30% within 30 years. The mortality from cirrhosis once that occurs is 2% to 5% per year. Hepatocellular carcinoma occurs at a rate of approximately 3% to 7% per year after the development of cirrhosis and in our transplant centers, HCV now accounts for 35% to 40%, and will probably soon approach 50%, of all liver transplants.

Liver Biopsy - Just Think About It

Emmet B. Keeffe, MD

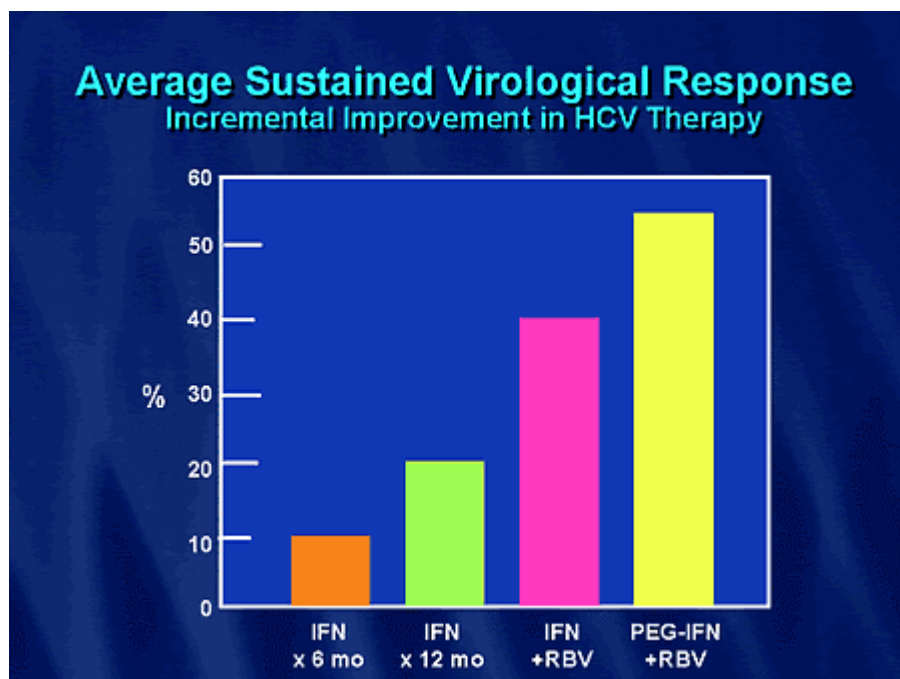
Role of Liver Biopsy in Hepatitis C

There are a number of potential arguments for and against routine biopsy. Let me address some of the arguments for a routine biopsy. You probably heard of some of these already from Dr. Fried. One is to determine the stage of fibrosis and, therefore, the need for therapy. The general recommendations that we practice is that if patients have stage 2, 3, or 4 fibrosis they're candidates for therapy. On the other hand, if they have minimal fibrosis, they probably do not need antiviral therapy.

Secondly, we may want to exclude unsuspected secondary diagnoses such as autoimmune hepatitis or nonalcoholic steatohepatitis (NASH). But the literature supports that these are uncommonly found.

Finally, biopsy may assist us in the management of side effects. If a patient is suffering through therapy with significant side effects and we know there is stage 3 or 4 fibrosis, we're more likely to use adjuvant therapy and push on. On the other hand, if we know there's minimal fibrosis, we may more likely abandon therapy.

The arguments against routine biopsy are really the thesis of my comments and they include several points. Number one is that we now have improved results of antiviral therapy particularly patients with genotypes 2 or 3 who can have as high as an 80% cure rate or a sustained virological response (SVR) rate. We also have risks and costs associated with liver biopsy. There's been a number of favorable cost-effectiveness analyses published in the literature that say that it's cost-effective to simply offer therapy to all patients rather than do a biopsy upfront. And finally, many patients prefer not to undergo a biopsy. I think it's a critically important point that we never hold off therapy in the patient that says, "Doc, I don't want to have a biopsy."



Slide 3. Average Sustained Virological Response: Incremental Improvement in HCV Therapy

This figure shows the remarkable progress in our treatment of HCV over the past 10 years from 1991 to current when our first therapy was officially licensed by the FDA; that is, interferon (IFN)

alpha-2b that was used for a 6-month course of therapy. The average SVR rate in those days was about 10%. We then learned from further investigations, particularly from our European colleagues, that if we treated longer for, 12 months or maybe even 18 months, we could increase the SVR rate to 20%. Then in 1998 with the introduction of IFN plus ribavirin (RBV), the SVR rate increased overall to 40% and now as of late 2001 with the licensure of pegylated interferon (PEG IFN) plus RBV, we're now up to a 55% overall SVR rate.

Treatment of Chronic Hepatitis C with Peginterferon and Ribavirin

	Pegasys ¹	PEG-Intron ^{TM2}
Overall	56%	54%
Genotype 1	46%	42%
Genotypes 2 & 3	76%	82%

¹Fried et al. *N Engl J Med* 2002; *In press*
²Manns et al. *Lancet* 2001; 358: 958

Slide 4. Treatment of Chronic Hepatitis C With Peginterferon and Ribavirin

This slide summarizes the result of the two pivotal trials of PEG IFN alpha-2a or *Pegasys* and PEG IFN alpha-2b or *Peg-Intron* in combination with RBV in the treatment of chronic HCV. As you can see, the results are very similar between the 2 drugs with an overall SVR rate of approximately 55%, a lesser response with genotype 1 ranging from 46% to 42% and with genotypes 2 and 3 ranging from 76% and 82%.

I would just like to propose that there is now a changing role for liver biopsy in our practice. We primarily use liver biopsy to stage fibrosis and grade inflammation and we less often use liver biopsy to either make or confirm a clinical diagnosis because of our outstandingly accurate virological, immunological and molecular genetic tests although there still are a few conditions, such as granulomas or allograft dysfunction, where a biopsy is necessary for a precise diagnosis.

Liver Biopsy Role in Diagnosis

- Spycher et al, BMC Gastroenterology 2001;1:12
 - Retrospective review, 1995-99, 365 biopsies
 - Diagnosis confirmed in 84.4%; diagnosis specified, changed or added in 8.8%, 6.8% and 10.5%
 - Biopsy led to change in management in 12.1%

Slide 5. Liver Biopsy: Role in Diagnosis

Let me just show you now a few recent publications looking at the role of liver biopsy in the diagnosis of chronic liver disease. This first paper was a retrospective review from 1995 to 1999 of 365 biopsies. The clinical diagnosis was confirmed in 84%. The diagnosis was specified, changed, or added in 8.8%, 6.8%, or 10%. The liver biopsy actually led to a change in management in only 12%.

Liver Biopsy Role in Diagnosis

- Andriulli et al, Dig Dis Sci 2001;46:1409
 - Questionnaire study of 535 patients with chronic viral hepatitis undergoing biopsy
 - Clinical vs histological diagnosis concordant in 84%; additional diagnoses in 3.7%
 - Knowledge of grade and stage considered valuable in 60% and 66%
 - Treatment with IFN not changed in 81%

Slide 6. Liver Biopsy: Role in Diagnosis

In another study published late last year in *Digestive Diseases in Science*, a questionnaire survey of gastroenterologists related to 535 patients who had chronic viral hepatitis undergoing liver biopsy was conducted. The clinical versus the histological diagnosis was concordant in

84% of patients. Additional new diagnoses were made very uncommonly in only 3.7% of patients. The gastroenterologists, however, felt that knowledge of the grade and the stage of disease was valuable in not all, but about two-thirds, of their patients. However, their treatment with antiviral therapy with IFN was not changed in the great majority, 81% of the patients.

**Liver Biopsy
Role in Diagnosis**

- Saadeh et al, Hepatology 2001;33:196-200
 - 126 patients with chronic hepatitis C
 - Additional suspected diagnoses confirmed in 3 of 47 (6.4%); unsuspected diagnosis found in 3 patients
 - Presence or absence of cirrhosis predicted in only 23% using a clinical discriminant score using platelets, ALT/AST ratio and INR (Bonacini)

Slide 7. Liver Biopsy: Role in Diagnosis

Finally, in a study from the Cleveland Clinic of 126 patients with chronic HCV, once again additional diagnoses were confirmed in 6.4% but unsuspected new diagnoses were hardly ever made in only 3 patients. However, the presence or absence of cirrhosis was predicted, not very accurately, by this group of investigators in only 23% using a discriminant score with platelets, ALT/AST ratio, and INR.

Liver Biopsy - Just Think About It

Emmet B. Keeffe, MD

Alternatives to Liver Biopsy for Predicting Advanced Fibrosis in Chronic Hepatitis C Patients

There's an increasing interest in the use of noninvasive predictors of advanced fibrosis as an alternative to liver biopsy in patients with chronic HCV. In particular, a number of clinical observations have indicated that splenomegaly or thrombocytopenia indicate advanced fibrosis; either stage 3 or stage 4 fibrosis.

In addition, an AST/ALT ratio greater than one predicts advanced fibrosis and if one uses an AST/ALT ratio of greater than one plus a platelet count less than 150,000, that also adds to the discriminant function (Pohl et al. *Am J Gastroenterol.* 2001;96:3142).

And finally, there have been reports in the recent literature of other more complex formulae, none of which are yet fully as accurate as we like to predict fibrosis. However, I would say we can get a very strong clue from simple things such as the platelet count and the AST/ALT ratio regarding the patients who are more likely to have advanced fibrosis (Bonacini et al. *Am J Gastroenterol.* 1997;92:1302; Imbert-Bismut et al. *Lancet.* 2001;357:1069).

Liver Biopsy - Just Think About It

Emmet B. Keeffe, MD

Rationale for Selective Utilization of Liver Biopsy for Hepatitis C

My colleague in practice, Dr. Gabriel Garcia, and I wrote a recent editorial making the point that we thought liver biopsies should be used selectively, rather than routinely, in patients with chronic HCV. We based this on a number of issues. The first is cost-effectiveness analyses suggesting that the best strategy is to offer therapy to all patients and not perform a biopsy routinely in every individual.

In addition, many patients, particularly those who have genotypes 2 or 3 and learn of the very high SVR rate, prefer empiric therapy no matter whether they have advanced fibrosis or minimal fibrosis.

On the other hand, a liver biopsy is helpful in selective patients if the fibrosis stage will influence their decision regarding therapy or if the patient simply desires an estimate of their prognosis based on the stage of fibrosis.

And, finally, although we're not used to thinking this way, we can also do a liver biopsy during therapy in the patient experiencing severe side effects to help us decide whether we push on with therapy and use adjunctive measures to complete the course of therapy or whether we abandon therapy (Garcia and Keeffe. *Am J Gastroenterol.* 2001;96:3053).

Let me now summarize and I'll begin by summarizing general points about liver biopsy. The usual indications for liver biopsy include elevated ALT levels of unknown cause, grading and staging chronic liver disease, and miscellaneous conditions such as allograft dysfunction. Liver biopsy remains essential to make certain diagnoses, for example, granulomas and to grade and stage chronic liver disease, if needed. Pain occurs in 20% to 30%, severe complications in 3 per 1000 and death, uncommonly, in 3 per 10,000.

Let me now summarize the use of liver biopsy in chronic HCV. Cost-effectiveness analyses show that the best strategy is to offer antiviral therapy without a biopsy. Many patients, especially those with genotypes 2 or 3 with an 80% cure rate, prefer empiric therapy no matter what their biopsy might show.

On the other hand, if it's important for a decision of whether to initiate or to continue antiviral therapy, then a biopsy is helpful, selectively, in those circumstances. And, therefore, an evolving strategy in our practices in chronic HCV patients is to use biopsy selectively rather than in everybody.

Abstracts

HCV - (Virtually) All Patients Should Be Treated

Douglas R. LaBrecque, MD

The first commercial hepatitis C (HCV) diagnostic test was released in 1990. Since that time, our knowledge of the natural history of HCV and the factors that affect progression of the disease has expanded rapidly. The World Health Organization has recognized HCV as a major public health problem. Over 170 million cases of chronic HCV infection are present throughout the world, with over 4 million chronic carriers of the disease in the United States. At least 20% of these patients will progress to cirrhosis and liver failure or develop hepatocellular carcinoma (HCC).

Although identification of the hepatitis C virus and the means by which it is spread have led to a decrease in the incidence of new cases of HCV, the prevalence of the disease will continue to rise for at least the next 15 years. Hepatitis C is already the leading reason for liver transplantation in the United States and Europe. The annual direct and indirect costs attributed to HCV in the United States in 1997 were \$5,460,000,000. These costs are also predicted to increase steadily as more patients reach the stage of cirrhosis and develop the complications of portal hypertension. Therefore, it is imperative that we find successful treatment for this often-fatal disease.

The emergence of steadily improving therapies for HCV and the growing recognition of the potentially serious consequences of this disease have led to strong differences of opinion within the medical community. One of the most basic arguments concerns who should be treated. Should all patients who carry the virus undergo treatment or should treatment be more selective?

The primary goal of therapy is to eradicate the virus. When the virus has been eliminated, disease progression ceases; symptoms, if present, usually improve; liver histology shows less inflammation and necrosis and, often, a decrease in fibrosis.

The best currently available therapy, pegylated interferon plus ribavirin, can achieve over 60% long-term virus eradication. This therapy is even more effective in patients with viral genotypes 2 and 3, who are successfully treated 70% to 90% of the time. If the virus cannot be eliminated, secondary goals of therapy are to slow disease progression, improve liver histology, reduce the risk of developing HCC, and improve the patient's health-related quality of life. Remarkably, treatment with interferon alpha, including the newer pegylated interferon alphas, has been shown to be of benefit in achieving all of these secondary goals as well. Several studies have also demonstrated that the therapy, while expensive, is also cost-effective. Thus, even if the primary goal of therapy to eliminate the virus is not achieved, most patients still benefit.

Therefore, I believe that virtually all patients with HCV should be treated. This would include all patients with significant fibrosis on liver biopsy; all patients with genotypes 2 and 3 (regardless of the degree of fibrosis); patients with severe symptoms or clinical cryoglobulinemia; and those patients who have special concerns and/or are very anxious to eliminate the virus. Therapy should be considered for patients with mild disease and compensated cirrhosis. Therapy may be deferred in patients who have hepatitis of long duration with minimal disease on biopsy (especially those with the harder to treat genotype 1); older patients with minimal disease; patients with other major medical problems who have only minimal liver disease; and those with absolute contraindications to treatment as listed in the package insert (eg, severe depression,

severe heart disease, etc). However, if therapy is deferred, the patient will require regular follow-up and repeat liver biopsy in 3 to 5 years to evaluate the progression of their disease.

Abstracts

HCV - The Case for Selective Treatment

Robert G. Gish, MD

Hepatitis C virus (HCV) has now become one of the most important causes of chronic liver disease affecting more than 4 million individuals in the United States, with a similar proportion in Japan and 170 million individuals worldwide with a chronic infection rate of more than 60%. The rate of disease progression in chronic HCV is variable and at least 20% of patients develop cirrhosis. There is no correlation with alanine aminotransferase (ALT) levels, viral load, or HCV genotype. However, later age at infection, alcohol consumption, fatty liver, male gender, increased liver iron, and coinfection with HIV and hepatitis B, have been associated with more rapid disease progression.

The burden of HCV is great in terms of morbidity and mortality, as well as associated costs to the healthcare system. Up to 10,000 deaths per year are expected in this decade due to HCV. Over the next 20 to 30 years, HCV-related mortality is expected to double. Direct and indirect medical costs for this period are estimated at \$10.7 billion and \$75.5 billion, respectively. A recent study estimates the current annual cost associated with HCV as \$5.46 billion, similar to that of asthma (\$5.8 billion). The liver biopsy is the best tool to determine who is at risk for progressive liver disease. Cirrhosis due to HCV infection is the cause of more than 50% of liver transplants. Currently more than 19,000 patients are awaiting liver transplantation, yet there are only 4900 livers available each year. A major concern to health care practitioners in California is the expected egress or retirement of up to 30% of physicians and the paucity of subspecialty practitioners. The load for managing HCV is shifting to primary care health providers who are in dire need of resources to combat this national and international scourge. It is important to note that currently there are more than 19,000 patients awaiting liver transplantation and more than 10,000 deaths per year are expected in this decade due to HCV at high costs to the healthcare system. Treatment should be focused on patients with advancing disease on liver biopsy, symptoms, highly motivated patients, and patients with extrahepatic manifestations of HCV infection.

Published cost-effectiveness analyses indicate that antiviral therapy with interferon, or interferon and ribavirin is economically beneficial and similar data are expected and have recently been released for PEG interferon and ribavirin combination therapy. Sustained clearance of serum HCV RNA of up to 64% after therapy has now been reported and is associated with both short- and long-term improvement in liver histology and may be associated with a decreased risk of liver cancer, liver transplant, and death. Patients have been followed for 5 to 15 years after completing therapy and more than 97% continue to have undetectable HCV RNA, normal liver tests, and histologic improvement.

Abstracts

Liver Biopsy - Just Do It

Michael W. Fried, MD

Liver biopsy remains the gold standard for the management of patients with chronic liver disease. Liver biopsy has multiple important roles for the evaluation of patients with chronic hepatitis C (HCV). The liver biopsy can be used to confirm the diagnosis, to grade and stage the extent of liver injury, to provide patients with important prognostic information, and to help select candidates for therapy. Although one can argue that certain roles of liver biopsy, ie, diagnosis of HCV, have been usurped by laboratory tests that unequivocally determine if a patient is infected with HCV, the information obtained by a liver biopsy will insure that the physician and patient understand their particular disease state. Liver biopsy may lead to additional unsuspected diagnoses such as nonalcoholic fatty liver disease or hemochromatosis. These entities have a great impact on the treatment and prognosis of HCV-associated liver disease.

The most important role for a liver biopsy, however, is the ability to accurately stage the extent of liver injury and fibrosis. Biochemical markers such as serum alanine aminotransferase (ALT) activity only loosely reflect the grade of necroinflammatory activity and do not correlate at all with stage of fibrosis. Markers of hepatic fibrosis, hyaluronic acid, procollagen III peptide, and other fibrosis-associated markers do have some value in predicting significant fibrosis. However, there is frequently significant overlap between mild and severe disease for individual patients to the extent that the specificity and sensitivity will never equal that of liver biopsy. Since the presence of fibrosis is the most important correlate of prognosis, absence of this information or inaccurate assumptions will hamper the clinical care of patients by denying them an accurate assessment of their liver disease. In this context, there are certain patients where liver biopsy is not needed to determine the stage of liver disease. Thus, those with clinical evidence of hepatic decompensation or evidence of cirrhotic portal hypertension will not benefit from additional confirmatory evidence that cirrhosis is present. Liver biopsy should be deferred in these patients unless the stage is unclear or management may be altered.

Several groups warrant special attention. Patients with persistently normal ALT generally have mild disease, although significant fibrosis has been reported, including cirrhosis in 3% to 5% of patients. Patients with hemophilia represent another unique population in whom liver biopsy may be performed safely, although with factor replacement and close consultation with hematologists.

As with any diagnostic test, the decision to perform a liver biopsy must be individualized after a discussion about the risks and benefits of the procedure. It cannot be overstated that liver biopsy is critical for accurate staging and for counseling patients with HCV. No other tests currently available can duplicate the information that can be obtained from a sliver of liver.

Abstracts

Liver Biopsy - Just Think About It

Emmet B. Keeffe, MD

The traditional gold standard to stage and establish the diagnosis of chronic liver disease is liver biopsy. Historically, liver biopsy was the primary test used in the diagnostic work-up of nearly all liver disorders. However, chronic liver disease can now be accurately diagnosed by the use of contemporary serological and virological tests for viral hepatitis, immunoserological tests for

autoimmune liver diseases, genetic tests for hereditary liver diseases, history and chronology of medication use for drug-induced liver disease, history of alcohol abuse for alcoholic liver disease, and typical phenotype (eg, obesity, diabetes mellitus, dyslipidemia) for nonalcoholic fatty liver disease.

All patients with chronic hepatitis C (HCV) who are candidates for antiviral therapy may not need to undergo a procedure for which there is much apprehension, a finite complication rate, and personal and societal costs. Several studies show that liver biopsy seldom yields new diagnoses in patients with chronic HCV. Thus, the primary role of liver biopsy is to grade and stage HCV, rather than exclude coexistent diseases. Some patients prefer to defer rather than undergo current therapy if they have no or minimal fibrosis (stages 0 or 1), but are agreeable to therapy if they have advanced fibrosis (stages 2 to 4). Other patients opt for therapy but also want to know their degree of hepatic fibrosis as a general indicator of prognosis. In both of these circumstances, a liver biopsy is helpful. However, as the outcomes of therapy have improved with the advent of peginterferon plus ribavirin - especially in patients with genotypes 2 and 3, more patients prefer empiric therapy in an attempt to achieve a sustained virological response irrespective of whatever a liver biopsy might show. In addition, cost-effectiveness analyses favor empiric treatment without prior liver biopsy. If a pretreatment liver biopsy is not performed and major side effects occur during therapy, liver biopsy can then be performed to assist in the decision regarding stopping vs. continuing therapy (absent or mild vs advanced fibrosis) and in the decision regarding the use of adjunctive therapies, eg, antidepressants, epoetin, or granulocyte colony stimulating factor (G-CSF), to facilitate completion of therapy.

It is of paramount importance that liver biopsy should not be a barrier to therapy; patients not desiring a biopsy should not be denied therapy. It is also important to make a distinction between physicians in private practice seeking a practical approach to the management of chronic HCV vs investigators at tertiary centers, who are enrolling patients in clinical trials. Thus, rather than using the "just do it" approach to liver biopsy, clinicians might want to embrace the "just think about it" approach in the context of clinical findings, patient preferences, and need to know fibrosis stage to make a decision regarding therapy.