CLINICAL DECISION-MAKING IN CHRONIC HEPATITIS C

INTERNAL MEDICINE GRAND ROUNDS

UT SOUTHWESTERN MEDICAL CENTER

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This is to acknowledge that Dr Malet has disclosed financial interests or other relationships with commercial concerns related directly or indirectly to this program. Dr. Malet will be discussing off-label uses in his presentation.

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Special interests...
Hepatitis C
Hepatitis B
fatty liver disease
health services research

Abbreviations used:

HCV...	hepatitis C virus
SVR...	sustained virologic response
EVR...	early virologic response
Peg-IFN...	pegylated interferon
RBV...	ribavirin

This Grand Rounds will address the decision-making process in the management of patients with chronic hepatitis C. The format will follow what is usually the scenario that temporally unfolds once a patient has been determined to have a positive antibody test for hepatitis C.

Ten of the key questions a physician poses to him/herself during the evaluation of such a patient are listed below. These do not represent all the questions or concerns that need to be addressed, but are an outline of the process that leads from initial discovery of the problem to its ultimate resolution vis-à-vis treatment. The management of patients with chronic hepatitis C is a challenge. Unlike many other forms of therapy, treatment for chronic hepatitis C can be viewed mainly as preventative, that is, with the aim of preventing progression to cirrhosis. The treatment is difficult and expensive (retail cost about $2000/mo) and most of the patients are asymptomatic; the success rate is under 50% for the majority of patients. Therefore, a careful weighing of the utility of therapy must be undertaken.

Each patient has a unique set of circumstances to consider and arriving at a mutually satisfactory treatment plan requires careful deliberation. The thoughts and desires of the patient are crucially important in the decision-making. Hopefully, this Grand Rounds will enable physicians to better understand the thought process that takes place in evaluating a patient for treatment of chronic hepatitis C.

10 key questions a physician asks him/herself in the care of a patient with chronic hepatitis C...

Question 1...	my patient has a positive hepatitis C antibody. Does he/she have chronic hepatitis C?
Question 2...	I now know my patient has chronic hepatitis C; what tests are useful in assessing his/her liver status?
Question 3...	is a liver biopsy always necessary?
Question 4...	how are the findings on liver biopsy used in the decision-making process regarding treatment?
Question 5...	using all the available information, how do I arrive at a recommendation regarding treatment to my patient?
Question 6...	I understand there are now 2 kinds of pegylated interferon; how do I decide which one to use?

Question 7...	is the treatment really as difficult as many patients believe?
Question 8...	how do I monitor my patient while on therapy?
Question 9 (part 1)...	my patient has remained virus-free for 6 months post-treatment; what does that mean for the long term?
(part 2)...	my patient has failed treatment; now what?
Question 10...	what are the prospects for new treatments that might be more effective and/or easier?

Each question will be addressed and as will be seen, there are few clear-cut answers. Most questions have a number of facets that merit examination and have a number of possible solutions. At the beginning of each section, the pertinent conclusions of the recent **NIH Consensus Development Conference** on the **Management of Hepatitis C** will be given.

NIH Consensus Development Conference

The NIH Consensus Development Conference was held in Bethesda, MD on June 10-12, 2002. The last such conference was held in March 1997 and since that time, significant advances had occurred. The purpose of this conference was to "examine the current state of knowledge regarding management of hepatitis C and identify directions for future research." In order to be able to put the findings of this conference in proper perspective, it is essential to understand the process of how this conference was organized.

During the first day-and-a-half of the conference, experts presented the latest knowledge about hepatitis C to an independent non-Federal panel. Of most interest were "the most recent developments regarding management, treatment options and the widening spectrum of potential candidates for treatment." None of the 12 panel members was an expert on hepatitis C and, in fact, only 5 were gastroenterologists. The others included a range of areas of expertise including internal medicine, geriatrics, ID, oncology, pediatrics, public health; a layperson was also a member. The purpose of this membership composition was to lessen the number and degree of pre-existing biases that hepatitis C experts might have had. Also, a wide variety of perspectives were represented and more emphasis on "the big picture" could be given.

After weighing all of the scientific evidence presented, the panel drafted a statement addressing 6 key areas:

1. What is the natural history of hepatitis C?
2. What is the most appropriate approach to diagnose and monitor patients?
3. What is the most effective therapy for hepatitis C?
4. Which patients with hepatitis C should be treated/
5. What recommendations can be made to patients to prevent transmission of hepatitis C?
6. What are the most important areas for future research?

On the final day of the conference, the draft statement was read to the audience and comments and questions followed. Thus, the final consensus statement is not an official policy statement of the NIH nor of the Federal Government. The final consensus statement of the panel was released on Sept. 12, 2002 and can be found at www.consensus.nih.gov or in the supplement to the November 2002 issue of Hepatology (Vol 36, no.5, suppl. 1). The statement is broad in its conclusions and leaves room for interpretation in a number of areas. It represents a 'snapshot in time" and will certainly change as time goes on. However, as a guideline for physicians and patients, it has accomplished its purpose as representing a consensus about the state of the art of management of chronic hepatitis C in June 2002.

Question 1
Q... my patient has a positive hepatitis C antibody. Does he/she have chronic hepatitis C?
A... probably yes, but not necessarily.

NIH Consensus Development Conference statement
On further evaluation of a positive HCV antibody test...
"a positive EIA (antibody) test should be confirmed by a qualitative HCV RNA assay with a lower limit of detection of 50 IU/ml or less".

On further evaluation of a negative HCV RNA test in a patient with a positive HCV antibody test...
"a single negative assay does not exclude viremia and may only reflect a transient decline in viral level below the limit of detection of the assay. A followup HCV RNA assay should be performed to confirm the absence of active HCV replication".

Hepatitis C antibody testing by EIA
The standard antibody test for hepatitis C (anti-HCV) is an enzyme immunoassay (EIA) assay. In 1990 the first generation anti-HCV EIA was developed and in 1992, the second generation. Currently, the third generation EIA assay is in use in most centers. A positive test represents exposure to the hepatitis C virus, which may

either be resolved or ongoing. The specificity of the EIA test is greater than 99% but is not 100%. Thus, false positive tests may occur.

A key to understanding the meaning of a positive anti-HCV test is the fact that those persons who acquire hepatitis C (that is, are infected) develop antibodies to hepatitis C and have a positive anti-HCV test. Approximately 20% of persons who develop acute hepatitis C spontaneously and permanently clear the virus. However, the antibodies to hepatitis C remain presumably life-long and, when tested, these persons will have positive anti-HCV test.

Therefore, apart from the acute infection, there are 4 categories of people who have a positive anti-HCV test:

1. those with chronic hepatitis C
2. those who had (acute) hepatitis C but cleared the virus
3. those with a false positive anti-HCV test
4. those who have cleared the virus after medical treatment

In summary, a positive anti-HCV test usually does, but not necessarily, indicate the presence of chronic hepatitis C. In all cases, further evaluation determining HCV RNA by PCR must be undertaken (there are other methods of determining HCV RNA, but PCR is the most common and will be exclusively referred to henceforth). Therefore, *a patient cannot be diagnosed as having chronic hepatitis C unless HCV RNA testing confirms the positive anti-HCV test.*

Before proceeding to the section on HCV RNA testing, a note must be made of false negative anti-HCV testing. The anti-HCV test by EIA has a greater than 99% sensitive in detecting HCV infection. EIA testing is, therefore, occasionally negative in patients with active HCV replication/infection. This has been well documented in some groups of immunocompromised patients, such as those with HIV/AIDS or undergoing hemodialysis. It must be strongly emphasized, though, that anti-HCV testing by EIA can be falsely negative in normal immunocompetent patients. So, if a patient has evidence of chronic hepatitis and the cause cannot be identified despite extensive evaluation, an HCV RNA test should be performed even in the face of a negative anti-HCV test by EIA.

HCV RNA testing by PCR

If there is a "gold standard" for determining HCV infection, it is measurement of HCV RNA. Having said this, there are limits to the detection ability for HCV using this methodology. There are currently 2 types of HCV RNA assays: qualitative and quantitative. The qualitative assay is more sensitive with a typical detection limit of 50 IU/ml. The typical detection limit for quantitative assays is about 600 IU/ml. International units (IU) have replaced copies as the units of HCV RNA assays and are

defined with reference to the WHO HCV RNA standard. False positive qualitative assays may occur on the order of about 1%.

Because of its greater sensitivity, the *qualitative* HCV RNA assay should be used to confirm a positive anti-HCV assay by EIA. In actual practice however, the quantitative HCV RNA assay is often used for confirmation if there is an extremely high index of suspicion for chronic hepatitis C. However, if this approach is used, and a negative result is found, a qualitative assay must then be used for further confirmation.

The *quantitative* HCV RNA assay is most useful during treatment of chronic hepatitis C with interferon and ribavirin (RBV). False positive and negative quantitative test results are rare. It is extremely important to note that there is no relationship between quantitative the level of HCV RNA and disease activity nor progression.

Hepatitis C antibody testing by RIBA

Lastly, mention should be made of another method of testing for anti-HCV, using the RIBA (radioimmunoblot assay) test. In years past, this test was used to confirm a positive anti-HCV test by EIA. In clinical practice today, the RIBA method is rarely used but does have 1 major utility, that of clarifying whether a positive anti-HCV by EIA result (i.e., unconfirmed by further HCV RNA testing) is a true or a false positive.

In a patient who had hepatitis C but spontaneously cleared the infection, both the EIA and RIBA tests will remain positive (HCV RNA will, of course, be undetectable). In the patient who never actually had hepatitis C, but showed a positive result on EIA testing, the RIBA test will be negative, thus demonstrating that the EIA result was a false positive. Knowing this latter result is generally quite comforting to a blood donor or person undergoing an insurance physical who was unexpectedly confronted with a positive EIA test result.

Summary...

- **Anti-HCV testing by EIA detects infection, past or present, with hepatitis C; it remains positive life-long whether or not the virus is still present.**
- **Determination of (qualitative) HCV RNA is the current "gold standard" for the diagnosis of chronic hepatitis C, that is, ongoing infection.**
- **HCV RNA levels determined using a quantitative assay are useful for assessing the effectiveness of antiviral therapy, but apart from this, have no relationship with disease activity nor progression.**

Question 2

Q... I now know my patient has chronic hepatitis C; what tests are useful in assessing his/her liver status?

A... liver enzymes and all the standard liver "function" tests, HCV genotype, AFP, abdominal ultrasonography, immune status to hepatitis A & B, tests to exclude other causes of liver disease.

NIH Consensus Development Conference statement

On the significance of ALT values ...

"a weak association exists between the degree of ALT elevation and severity of the histopathological findings on liver biopsy. ALT levels are insensitive in detecting disease progression to cirrhosis"

On normal ALT values...

"Patients who initially have a normal ALT level should undergo serial measurements over several months to confirm the persistence of normal ALT levels."

On noninvasive tests of fibrosis...

"No single test or panel of serologic markers can provide an accurate assessment of intermediate stages of hepatic fibrosis. Similarly, quantitative tests of liver function and radiologic imaging of the liver are sensitive for diagnosing advanced cirrhosis but are not useful in assessing hepatic fibrosis and early cirrhosis."

Clinical evaluation of patients with chronic hepatitis C

Suffice it to say that clinical expertise and acumen should direct the evaluation. Many patients, if not most, with chronic hepatitis C are asymptomatic. Many others have nonspecific symptoms such as fatigue, body aches, decreased energy, etc. The physical examination might provide some findings suggestive of hepatic impairment, but is normal in the great majority of patients with chronic hepatitis C.

Not all laboratory tests need to be performed in every patient, while more extensive testing than usual may be required in some patients. The main aim of the initial clinical evaluation of a patient with chronic hepatitis C is to determine the degree of hepatic functional impairment. Most hepatologists would agree that a thorough evaluation to exclude other potential causes of liver disease is worthwhile. This would include tests for iron overload, autoimmune hepatitis, hepatitis B, alpha-1-antitrypsin deficiency and several other conditions depending on the situation.

Liver enzymes...ALT & AST

There is no linear relationship between height of ALT and AST and disease activity. Serum transaminase levels often fluctuate over time and may drop below the upper

limit of normal transiently. Rarely are enzyme levels over 300 in chronic hepatitis C. An AST/ALT ratio >1 can be seen with cirrhosis but is not specific.

As discussed below, persistently normal or 'mostly' normal transaminase levels may be seen in a small proportion of patients. Depending on the population examined and the definition of 'persistently normal', the prevalence of persistently normal transaminase levels may be in the range of 10 to 20 %. Although there are some implications to this finding, in terms of a lower average stage of fibrosis, the trend is to evaluate such patients in the same way as those with elevated liver enzymes.

Other liver 'function' tests

Bilirubin, albumin and PT/INR are, of course, useful in assessing functional liver status. Abnormalities in these tests are virtually only seen in those with advanced fibrosis or cirrhosis (METAVIR fibrosis stages 3 and 4). Elevations of serum bilirubin, particularly if mild, should be further evaluated with an indirect bilirubin level to assure that Gilbert's syndrome is not the cause. Although informative when abnormal, in the majority of patients with advanced fibrosis or cirrhosis, these tests (bilirubin, albumin and PT/INR) are normal.

A decreased platelet count may be a reflection of hypersplenism due to portal hypertension. A number of attempts to use combinations of laboratory tests to predict the presence of advanced fibrosis or cirrhosis have been made. In some of these studies, a decreased platelet count (using various cut-offs from 120,000 to 80,000) has been shown to be perhaps the single best predictor of significant fibrosis. However, whether using a combination of lab studies or the platelet count, the sensitivity and specificity of these tests is suboptimal.

Abdominal ultrasonography

Ultrasonography is useful in detecting signs of hepatic fibrosis such as increased echogenicity and a nodular contour. However, increased liver echogenicity may be due to fibrosis or fat or a combination and ultrasonography is not very good at distinguishing these. In addition to hepatic texture features, the presence of splenomegaly, ascites or varices can be detected and are fairly specific signs of advanced fibrosis. Liver masses, such as hemangiomas and hepatocellular carcinoma (HCC) can also be detected. Further evaluation of liver masses requires the use of MR or CT scanning.

HCV genotype

Determining the HCV genotype is important so as to be able to be able to fully discuss the pros and cons of treatment options with the patient. The HCV genotype is the single most important determinant of ultimate treatment success (sustained virologic remission [SVR] for genotype 1... 45%±, for genotypes 2 & 3... 75-80%±).

It must be determined in all patients in whom treatment is being contemplated. In those patients in whom treatment is not under consideration, genotype determination is not necessary. There is no direct relationship between HCV genotype and disease activity nor progression.

Immunity to hepatitis A and B

Patients with chronic hepatitis C are at increased risk for fulminant hepatitis if superinfected with hepatitis A or B. A total anti-HAV and anti-HBs & HBc should be determined to assess immunity and to guide vaccination strategies. In patient populations where there is a low prevalence of anti-HAV positivity, antibody screening may be bypassed and a universal vaccination strategy may be employed. In patients with chronic hepatitis C who are being considered for listing for liver transplantation, immunity against hepatitis A & B is a mandatory requirement.

Persistently normal liver enzymes

Approximately 10 to 20% of patients with chronic hepatitis C have persistently normal ALT and AST levels. The prevalence depends on the population studied and the definition of persistently normal. The definition of persistently normal in various studies has been variable. On first presentation, more than 20 or 30% of patients may have normal levels, but with serial follow-up over 1-2 years, many (approximately 50-70%) of these have at least 1 set of elevated values. This period of follow-up may not be long enough, however. In one study (7), patients with normal ALT levels were serially followed with tests every 2 months. It was only after the 4th year of follow-up that no further patient showed an ALT elevation.

Consequently, although many investigators would minimally define "persistently normal ALT and AST levels" as normal levels on at least 4 consecutive determinations over a 12 month period, a longer period of observation is probably warranted. The focus on normal ALT levels is related to the finding that such patients, on average, have a somewhat lower stage of fibrosis on biopsy. However, a significant minority of such patients (about 20%) have advanced fibrosis (stages 3 or 4).

Summary

- **Determination of HCV genotype is essential in those being evaluated for treatment**
- **Abnormal lab tests such as low platelet count, albumin or elevated bilirubin or PT/INR are useful in detecting patients with advanced fibrosis but are not abnormal in many or most such patients.**
- **Normal ALT and AST levels may be seen at initial presentation of some patients, but with follow-up, many such patients demonstrate elevated levels.**

Question 3

Q... is a liver biopsy always necessary in assessing a patient with chronic hepatitis C?

A... not always, but it does provide very useful information and authorities would recommend it in most situations.

NIH Consensus Development Conference statement

On liver biopsy ...

"Liver biopsy provides a unique source of information on fibrosis and assessment of histology. The information obtained on liver biopsy allows affected individuals to make more informed choices about the initiation or postponement of antiviral treatment. Thus, the liver biopsy is a useful part of the informed consent process."

"In general, a baseline assessment of liver histology offers a valuable standard for subsequent comparisons (in those who remain untreated or who fail treatment*). However, the appropriate interval for subsequent evaluations is yet to be determined."*

On liver biopsy in patients with HCV genotypes 2 or 3 ... "Since a favorable response to current antiviral therapy occurs in 80% of patients infected with genotype 2 or 3, it may not always be necessary to perform liver biopsy in these patients to make a decision to treat. The usefulness of a pretreatment liver biopsy in this group ... requires further study."

Fibrosis in chronic hepatitis C begins in the portal tract and then extends peri-portally into the lobules. The fibrosis then further extends (bridges) towards the central veins. Cirrhosis ensues when the bridging fibrosis between portal areas and central veins becomes extensive and regenerative nodules form.

Fibrosis Staging Systems

METAVIR system... most commonly used in clinical practice

Stage 0	no fibrosis
Stage 1	portal tract fibrosis
Stage 2	portal and peri-portal fibrosis
Stage 3	bridging fibrosis
Stage 4	cirrhosis... architectural distortion with nodules

Ishak system... used in some research studies

Stage 0	no fibrosis
Stage 1	portal tract fibrosis

Stage 2	portal tract and peri-portal fibrosis
Stage 3	mild bridging fibrosis
Stage 4	bridging fibrosis with some architectural distortion
Stage 5	mild cirrhosis
Stage 6	established cirrhosis

One of the central issues in the evaluation of patients with chronic hepatitis C is whether or not to perform a liver biopsy to precisely stage and grade the disease. Staging refers to the fibrosis stage since this is a key, if not the key, prognostic factor. In addition, the grade of inflammation can also be determined which in some cases (higher grades) also influences the recommendation with regard to treatment. In the majority of patients with chronic hepatitis C being evaluated for treatment, most authorities recommend that a liver biopsy should be performed.

Some specific questions that a liver biopsy is useful in answering are:

1. Is fibrosis present?
2. If so, what is the stage of fibrosis?
3. What is the grade of inflammation?
4. Can an estimate be made of the rate of progression of the fibrosis? or, stated another way, is the patient at risk for developing cirrhosis?
5. Based on the stage of fibrosis and other clinical factors, is treatment warranted now or in the near future or can it be postponed, either temporarily or indefinitely?
6. If treatment can be postponed, what is the baseline liver histology against which future liver biopsy results can be compared?
7. Is the patient at risk for HCC (is cirrhosis present?) and should a screening program for HCC be implemented?
8. If the patient has failed previous treatment, does the current stage of fibrosis justify another attempt at therapy?

The exact proportions of the 4 METAVIR stages of fibrosis (or no fibrosis) in groups of patients with chronic hepatitis C has not been determined in large cross-sectional groups of patients. Based on selected patients in multicenter trials, most patients with chronic hepatitis C who undergo liver biopsy as part of their evaluation will have intermediate stages of fibrosis... i.e., stage 1 or 2. However, smaller but important proportions have stages 0, 3 or 4. One major advantage of liver biopsy is that, in some cases, it may diagnose cirrhosis or advanced fibrosis where it was previously unsuspected; this finding will greatly influence treatment advice. Conversely, biopsy may demonstrate no fibrosis in some cases and thus obviate or lessen the need for treatment, depending on the clinical circumstances.

Liver biopsy and HCV genotypes 2 & 3

Currently, there is a re-thinking taking place about the necessity for liver biopsy in patients with HCV genotypes 2 and 3. These genotypes have the highest SVR with Peg-IFN + ribavirin, about 75-80% after 24 weeks of therapy. For those who tolerate the medications at full or near full dosage and who finish the full course of therapy, the SVR can approach 90%. Investigators are now questioning whether proceeding to treatment without the biopsy should be now recommended.
The downside of this approach is that some patients with no fibrosis or very slowly progressive fibrosis will be treated, perhaps unnecessarily depending on one's concept of "unnecessary".

When would a liver biopsy not be clearly warranted?

- Relatively recent acquisition of disease, e.g., within 5 years, in which case fibrosis probably won't be present yet
- Previous liver biopsy already showing advanced fibrosis (stage 3 or 4)
- When there is no realistic chance for treatment because of serious comorbid illnesses, etc.
- When the patient declines to have one
- When a patient declares that he/she wishes to be treated regardless of what the biopsy shows
- When a serious coagulation disorder is present
- High probability of cirrhosis based on physical exam, labs and radiologic studies. This is a somewhat subjective decision that depends on agreement between the physician and the patient that the evidence for advanced fibrosis is strong enough to obviate the need for a biopsy.

Question 4

Q... how are the findings on liver biopsy used to determine what course to recommend to my patient?

A... the stage of fibrosis is key, especially when it can be correlated with the duration of infection.

NIH Consensus Development Conference statement

On using liver biopsy results to decide who should be treated ...
"Treatment is recommended for patients with an increased risk for developing cirrhosis. These patients are characterized by a liver biopsy with portal or bridging fibrosis, and at least moderate inflammation..."

Fibrosis is generally regarded as irreversible (without treatment) and progressive once it starts. The rate of progression of fibrosis, however, varies widely from patient to patient. Some patients never develop any fibrosis while others progress

to cirrhosis in as little as 15 years. Most patients lie in between these two extremes. While some factors like age at acquisition of infection, male gender and excessive alcohol use have been associated with more rapid progression of fibrosis when groups of patients have been studied, the rate of progression cannot be predicted in any particular individual patient without a liver biopsy.

There are some questions now being raised (15) as to whether fibrosis may regress spontaneously or remain stable for prolonged periods of time. There are also questions being posed as to whether fibrosis progresses linearly or not and whether the rate of progression may accelerate in the later stages. These questions and others concerning fibrosis progression are being examined in prospective longitudinal studies.

Calculating the rate of fibrosis progression

Thierry Poynard's group in France have published (14) calculated rates of fibrosis progression from cross-sectional population studies using a single liver biopsy and estimated duration of infection. The duration of infection can be calculating from the presumed date of infection if a clear risk factor can be identified. Obviously, this is not possible in all cases since an identifiable risk factor is not present. With this limitation, though, *the average rate of fibrosis progression was determined to be 0.13 METAVIR stages per year.*

In this study, the rate of progression varied widely among different patient groups. For example, the rate was higher in men vs women (0.15 vs 0.11 stages/yr), in those infected at an older age [>50 yo] vs younger [<20 yo] (0.33 vs 0.09 stages/yr) and in those with heavy [>50 gm/d] alcohol use vs no alcohol use (0.17 vs 0.12 stages/yr). This type of cross sectional retrospective study has a number of limitations but does is useful for discussing disease progression and the utility of treatment with a patient.

More recent data has been presented from 3 centers (16-18) in which a total of 338 patients with chronic hepatitis C underwent 2 liver biopsies from 3 to 8 years apart and the rate of progression of fibrosis was calculated. The average rate of progression was similar to the 0.13 stages/yr calculated by Poynard et al. In the 2 studies (16,17) in which biopsies were performed about 3 years apart, 32 & 39% of the patients had progression, the great majority of which was just 1 stage. In the other study (18) in which the biopsies were 8 years apart, 59% had progression; about half of these progressed 1 stage and the others 2 or 3 stages. Thus, progression does not take place in a uniform fashion among patient groups. Some patients progress, while others show no progression, up to 40% with no progression after 8 years in the Alberti et al (19) report. This once again shows that the rate of progression of fibrosis in any single patient cannot be accurately predicted by

comparing to rates observed in groups of patients; these group rates should only be used as an estimate. Serial liver biopsies in an individual patient represent the only conclusive way of determining the true rate of progression.

Liver biopsy and persistently normal ALT & AST

In a study from New Mexico (20), 75 patients with chronic hepatitis C and persistently normal ALT & AST levels (4 normal values within 12 mos) underwent liver biopsy. Results were compared with 200 patents chronic hepatitis C patients with elevated ALT & AST. *No patient in the normal liver enzyme group had a normal liver biopsy* but they did, as a group, have less severe histologic findings compared to the elevated enzyme group. The mean fibrosis stage (using the 6 fibrosis stage Ishak system, not the 4 stage METAVIR system) in the normal enzyme group was 1.4 ± 1.7 (SD) and 6% had cirrhosis. This compared to a mean fibrosis stage of 2.05 ± 1.6 ($p<0.05$) and a 19% cirrhosis prevalence in the other group.

The rate of fibrosis progression was calculated in both groups using patients in whom the duration of infection could be estimated (patients with identifiable well defined risk factors). The rate of progression (Δ in fibrosis stage per year) was 0.08 ± 0.07 in the normal enzyme group vs 0.15 ± 0.1 in the elevated enzyme group ($p<0.001$). A similar difference was noted after excluding those with significant alcohol consumption (>50g/day): 0.05 ± 0.06 vs 0.11 ± 0.10, ($p<0.001$).

These results are in agreement with 2 other studies (21-22) but another study (23) showed a higher mean fibrosis stage in normal enzyme patients. Thus, patients with normal enzymes have abnormal liver biopsies and are not to be considered "carriers" or as having "inactive disease". Some of these patients, in the range of 20%±, have advanced fibrosis or cirrhosis and these patients are usually not identifiable except by performance of a liver biopsy. The rate of progression of fibrosis in the normal enzyme patients appears to be about half that of those with elevated enzymes, but there is significant variability.

Therefore, the main benefit of a liver biopsy is that it provides a clear picture of the degree of fibrosis and inflammation present. Without a liver biopsy, the patient and the physician are not fully informed about the rate of progression of the disease and its prognosis. Decisions might be made to treat in cases where it may not be necessary; for example, in a patient with stage 0 fibrosis after 25 years of infection. Conversely, without a liver biopsy, a decision to postpone treatment may be made where it should be initiated without delay, such as in any patient with stage 3 or 4 fibrosis almost regardless of their presumed duration of infection. For a patient to be able to give a truly informed consent to treatment, in most cases, knowing the stage of fibrosis and an estimate of disease/fibrosis progression would appear to be optimal. However, because of the variation in patient preferences, some patients

may still wish to proceed with treatment even with no or minimal fibrosis. Others may choose to postpone treatment even with advanced fibrosis.

Summary...

- **The stage of fibrosis is the most important feature on biopsy**
- **Most patients with persistently normal ALT and AST have milder liver fibrosis; however, a small but important percentage have advanced fibrosis or cirrhosis.**
- **When stage 4 fibrosis (cirrhosis) is present, the prognosis is poor and every effort should be made to eradicate the virus. Stage 3 fibrosis is one step away from cirrhosis and a similar intense effort should be made to treat.**

Question 5

Q... using all the available information, how do I arrive at a recommendation regarding treatment to my patient?

A... the decision-making process is a combination of the patient's preferences and overall medical condition, and the treatment approach of the physician.

NIH Consensus Development Conference statement

On which patients should be treated ...

"All patients with chronic hepatitis C are potential candidates for antiviral therapy. Numerous factors must be considered in recommending treatment.

On treatment of patients with co-existing illnesses...

"Randomized controlled trials need to be carried out in special populations of patients not represented in current trials." ..."to define the best approaches to treating HCV in active drinkers, prisoners, those co-infected with HIV, patients with concurrent renal disease and patients with major psychiatric illness." and *... "patients in drug treatment programs, with decompensated cirrhosis and patients with adherence problems."*

Some factors to consider in deciding about treatment...

HCV/liver related

- presumed duration of infection
- stage of fibrosis
- rate of progression of fibrosis
- HCV genotype
- state of hepatic compensation

Patient related

- symptoms
- age
- phase of education/career... is now a good time for difficult treatment?
- other illnesses
- social issues... family, prison, homeless, adherence
- insurance/financial issues
- abuse issues... drug, alcohol, other

Physician related

- attitude towards treatment
- expertise
- access to experts/research investigators... for difficult cases

Physician attitudes about management... Physician attitudes towards treatment are not uniform. In attempting to arrive at a strategy for deciding about whether to offer treatment to a patient with chronic hepatitis C, various treatment approaches exist. Based on his/her interpretation of evidence and other factors, a physician may have formulated an opinion to:

1. offer treatment to all patients with chronic hepatitis C unless an obvious contraindication exists
2. offer treatment to those patients who have shown any signs of disease progression, i.e., even mild fibrosis on liver biopsy after decades of infection
3. offer treatment to those who are at risk for progressing to cirrhosis based on the calculated rate of fibrosis progression
4. offer treatment based on a combination of the presumed rate of disease progression, the patient's overall medical, social and psychological status and the assessment of any other factors that may influence the patient's projected life-span and their ability to tolerate the treatment.

Although the last is the most common physician approach patients will encounter, the other approaches will be encountered and will influence the advice the physician gives.

Patient attitudes about management... Patients, of course, have the ultimate say in the treatment decision process and have a range of opinions regarding the value of treatment. Preferences of patients are a reflection of their own unique psychological, cultural and social belief systems. Some common patient opinions about treatment are:

1. desire for treatment regardless of the specifics regarding disease progression since their main wish is to eliminate/kill the virus. Examples of reasoning like this are those who fear transmission to their spouse, who blame the virus for their symptoms such as fatigue or who want to be able to consider themselves 'healthy' and not infected by a virus. Other reasons include the desire to 'tackle the problem' now 'before it gets worse' or the lack of interest in following the disease progression with repeat liver biopsies, etc.
2. desire for treatment only if there is definite evidence of fibrosis
3. desire for treatment only if it is deemed 'absolutely necessary'
4. no desire for treatment using standard medications and instead use other non-standard treatments
5. desire for treatment based on the physician's advice

Thus, the discussions concerning the optimal treatment approach for an individual patient start out with pre-existing physician and patient beliefs. Patients' philosophy with regard to the advisability of therapy may or may not coincide with their physician's. Productive discussions can ensue once these beliefs are verbalized and the extent of the evaluation necessary can be decided upon. This particularly relates to whether a liver biopsy is to be performed or not. Most physicians, but not all, would recommend one and most patients would agree to have one since the information it reveals is key to the decision-making process. However, as described above, some physician beliefs, such as the advisability for treatment for all patients unless an obvious contraindication is present, relegate the role of a liver biopsy to a minor one. Similarly, patients who want treatment regardless of disease progression usually do not see the utility of a biopsy.

Role of co-existing medical or psychiatric diseases...

The goal of therapy for chronic hepatitis C is to prevent progression to cirrhosis or, if cirrhotic already, to prevent worsening of the fibrosis. The implied goal (not yet proven) is to prevent the patient's life-span from being shortened by the complications of cirrhosis such as hepatocellular carcinoma, ascites, variceal bleeding, generalized liver failure or encephalopathy. If the patient has another co-existing illness(es) that will presumably shorter his/her life-span, it is incumbent on the physician to make an educated evaluation as to whether the progression to cirrhosis or the other illness(es) will likely result in the patient's demise first. This clearly involves subjective decisions since the natural history of any illness cannot be accurately predicted in any individual patient.

For example, if a 45 year old patient with chronic hepatitis C, stage 3 after presumed 20 years of infection also has had diabetes mellitus for 3 years with no apparent complications, the decision to recommend treatment for the hepatitis is fairly easy. However, if that same patient has had diabetes for 18 years and has a serum creatinine of 2.1 and grade 2-3 retinopathy, what is the likelihood that

eventual cirrhosis will be a more serious health impairment than diabetic complications? There are a virtually infinite number of such scenarios that could be (are) encountered in which the 'answer' regarding treatment for the hepatitis is not straightforward.

Patients enrolled in large clinical research studies do not necessarily represent the general population. Results from such studies may or may not or may accurately reflect results achieved in clinical practice. The large multicenter studies cited as the basis for recommending the current treatment with pegylated interferon (Peg-IFN) and ribavirin (RBV) have not included patients with: more serious medical or psychiatric diseases, HIV, cancers, active drug or alcohol abuse, mental disabilities, renal impairment, organ transplantation and a variety of other conditions. Also not included are prisoners, the homeless and the elderly, Thus, data is lacking regarding the feasibility and efficacy of the current treatment in settings like these. Physician judgment and experience is essential for deciding about appropriate treatment recommendations in these situations.

Depending on the clinical scenario, stage of fibrosis and the preferences of the patients & physician, some possible decisions that may be made regarding treatment...

1. Treat now/soon
2. Treat in a research study
3. Treat within a year or two
4. Postpone for a variable time the final decision whether to treat or not
5. Wait for several years for newer treatment to become available
6. Observe & repeat liver biopsy in 3 to 5 years; decide about treatment then
7. Not a candidate for treatment, either temporary or permanent

Question 6

Q... I understand there are now 2 kinds of pegylated interferon; how do I decide which one to use?

A... they both give about the same result.

NIH Consensus Development Conference statement

On treatment with pegylated interferon plus ribavirin ...

"SVR rates were similar with both forms of pegylated interferon (alfa-2a and alfa-2b) when used in combination with ribavirin."

The standard of care now in treating chronic hepatitis C is with the use of subcutaneously administered pegylated interferon plus oral ribavirin. The Peg-IFN is administered once weekly and the ribavirin daily. The attachment of a polyethylene glycol molecule to the interferon substantially prolongs its duration of action. This

recent therapy has supplanted the former therapy consisting of thrice weekly standard interferon plus ribavirin daily (this combination therapy was known as Rebetron).

There are 2 forms of PEF-IFN, 12 kD Peg-IFN alfa 2b (Peg Intron, Schering-Plough) and 40 kD Peg-IFN alfa 2b (Pegasys, Hoffmann-LaRoche). There have been 2 pivotal studies (32,33) published on the use of 48 weeks duration therapy using Peg-IFN plus ribavirin for chronic hepatitis C compared with Rebetron. A 3rd important study (34) comparing 24 and 48 weeks treatment with PEG-IFN plus RBV has been published only in abstract form.

Sustained virologic response (SVR) defined as undetectable HCV RNA 24 weeks after end-of-therapy. Each treatment regimen given for 48 weeks.

	Rebetron	1,5 ug/kg Peg-IFN a-2b + 800 mg/d RBV	180 ug Peg-IFN a-2b + 1000-1200 mg/d RBV
Manns et al (ref 33)	47% n=505	54% n=511	
Fried et al (ref 32)	44% n=444		56% n=453

In these 2 studies, the results of treatment for the different HCV genotypes were 42 to 44% for HCV genotype 1 and 78 to 80 % for genotype 2 and 3. Thus, the results of 48 weeks of treatment of these 2 regimens with Peg-IFN plus ribavirin are quite comparable.

In the study by Hadziyannis et al (34), the effect of PEG-interferon alfa-2a (180 ug/wk) plus different doses of ribavirin for 24 vs 48 weeks of treatment were examined in groups according to their HCV genotype. 1284 patients were randomized into one of 4 groups:

1. PEG-interferon alfa-2a plus 800 mg/d ribavirin for 24 weeks
2. PEG-interferon alfa-2a plus 800 mg/d ribavirin for 48 weeks
3. PEG-interferon alfa-2a plus 1000 (<75 kg) or 1200 mg (≥75 kg)/d ribavirin for 24 weeks
4. PEG-interferon alfa-2a plus 1000 or 1200 mg/d ribavirin for 48 weeks

Results (SVR) by duration of treatment & HCV genotype

PEG-interferon alfa-2a +		genotype 1	genotype 2, 3
ribavirin 800 mg/d	24 wks	29%	78%
ribavirin 1000-1200 mg/d	24 wks	41%	78%
ribavirin 800 mg/d	48 wks	40%	73%
ribavirin 1000-1200 mg/d	48 wks	51%	77%

These results clearly demonstrate that patients with HCV genotype 2 or 3 only require 24 weeks treatment and that 800 mg ribavirin daily is sufficient. Patients with HCV genotype 1 require 48 weeks treatment to achieve the highest SVR and need 1000 or 1200 mg ribavirin daily. It should be noted that these results were obtained using PEG-interferon alfa-2a, not alfa-2b, but there is no reason to believe the results are not generalizable.

Summary...

- **Either form of pegylated interferon combined with ribavirin provides equivalent SVR's.**
- **Treatment is required for 48 weeks in those with HCV genotype 1 and for 24 weeks with HCV genotypes 2 & 3.**
- **A lower dose of ribavirin can be used for patients with HCV genotype 2 or 3.**

Question 7
Q... is the treatment really as bad as many patients believe?
A... no, but virtually all patients experience some side effects.

NIH Consensus Development Conference statement
On side effects of treatment... "The education of patients, their family members, and caregivers about side effects and their prospective management is an integral aspect of treatment."

Side effects of treatment with pegylated interferon and ribavirin are virtually universal and can affect almost any organ system. Some of those with over a 20% incidence in the multicenter trials are: fatigue, cytopenias, various neuropsychiatric symptoms, headache, insomnia, myalgias/arthralgias, nausea/anorexia, weight loss, skin rash, fever/rigors, alopecia, irritability, injection site inflammation. Some of these, like fever/rigors & myalgias/arthralgias, are temporally related to the injection

of interferon and tend to diminish over time. There are myriad other potential side effects that occur less commonly. Some deaths have been reported, usually due to infection, stroke, myocardial infarction or suicide.

The management of side effects usually involves a combination of temporary dose reduction and supplemental medications. Commonly used medications are NSAID's, SSRI's, antihistamines & sleeping aids. On occasion, Procrit/Epogen or Neupogen may be used for serious cytopenias. Despite sometimes intensive efforts at amelioration, about10% of patients discontinue therapy due to side effects.

Question 8
Q... how do I monitor my patient while on therapy?
A... the key is the quantitative HCV RNA value after 12 weeks.

NIH Consensus Development Conference statement
On monitoring treatment of patients with pegylated interferon plus ribavirin ...
"Early viral response (EVR), defined as a minimum 2 log decrease in viral load during the first 12 weeks of treatment, is predictive of SVR and should be a routine part of monitoring patients with genotype 1. Patients who fail to achieve an EVR at week 12 of treatment have only a small chance of achieving an SVR even if therapy is continued a full year. Treatment need not be extended beyond 12 weeks in these patients."

The goal of therapy is to eradicate the hepatitis C virus, that is, achieve a sustained virologic response. Data (serum HCV RNA levels) derived from viral kinetic studies and from large treatment studies has been used to identify those patients who will not achieve an SVR. Such monitoring practices have been utilized since the initial treatment with interferon monotherapy when it was shown that patients who were still positive for HCV RNA after 12 weeks of therapy had little chance for an SVR and, therefore, therapy should be discontinued. Similarly, during treatment with Rebetron, those who were still HCV RNA positive at 24 weeks had a very low likelihood (only about 1%) of an SVR with a further 24 weeks of treatment and were discontinued from therapy. Such "stopping rules" were, and still are, primarily focused on the negative predictive value of follow-up HCV RNA measurements. (Positive predictive values derived from HCV RNA decreases during treatment are less useful since there are always relapsers after the end of therapy.) No such early stopping rule has 100% predictability, as an occasional patient will have an SVR with further treatment. However, early stopping guidelines offer a balance between further fruitless treatment of many patients vs achievement of an occasional SVR. The term 'early virologic response' (EVR) has come into use to describe the degree of decrease of HCV RNA (by ≥2 logs or to undetectable) during treatment.

The results of treatment for patients in the 2 large multicenter studies (32,33) using pegylated interferon and ribavirin have been analyzed (38) to determine predictions for ultimate success (SVR) or failure (no SVR). A total of 965 patients, 446 with HCV genotype 1 and 277 with genotype 2 or 3 were examined for EVR; 529 (55%) achieved an SVR. Various definitions of EVR were examined. The aim was to ascertain what is the optimal time to determine EVR and at which time point does EVR best predict non-response to therapy. EVR at 12 weeks (defined as HCV RNA decreased by ≥2 logs or to undetectable) was found to have optimal characteristics. The negative predictive value (probability that an SVR will not be attained) based on failure to achieve an EVR after 12 weeks of treatment was 0.98 (range 0.96-0.99). This means that 98% of patients who fail to achieve this drop will fail to achieve a sustained remission after 48 weeks treatment.

Further examining this data, 81.6% of the 965 patients achieved a 2 log or greater drop in HCV RNA at 12 weeks, that is, an EVR; 19.4% (187 patients) failed to achieve an EVR (almost all had HCV genotype 1). Of these 187, only 3 achieved an SVR after the entire 48 weeks of treatment. If treatment had been discontinued based on not achieving an EVR, only these 3 patients (0.6% of 529 with an SVR) would have been prevented from achieving an SVR. Thus, the negative predictive value of an EVR is 98.4%. [If only HCV genotype 1 patients were analyzed, the negative predictive value is even higher, 99%]. For patients with HCV genotypes 2 and 3, 96% achieved an EVR, so it is probably not useful concept in these patients and treatment should be continued for 24 weeks in all.

In the above analysis, would it be worth continuing treatment for another 36 weeks in 187 patients only to achieve an SVR in 3? The physician and the patient ultimately decide whether treatment is worth continuing. Some physicians believe that full courses of therapy, although not successful in achieving an SVR, may be useful in decreasing inflammatory activity in the liver and perhaps slowing the progression of fibrosis. This is unproven and studies are ongoing. However, if the goal of treatment is eradication of the virus, the use of the EVR concept to guide stopping treatment appears to be useful for patients with HCV genotype 1.

Summary...

- **Measurement of quantitative HCV RNA is the single best predictor of response to therapy. The magnitude of decrease of the value after 12 weeks of therapy is highly predictive of ultimate success or failure.**

Question 9 (part 1)
Q... my patient has remained virus-free for 6 months post-treatment; what does that mean?

A... there is about a 99% likelihood that the virus will not return.

Durability of sustained virologic response...
Those who achieve an SVR have about a 99% chance that they will remain viral-free (42).

Impact of treatment on liver histology...
Liver-related mortality occurs almost exclusively among those with cirrhosis. So, an important benefit of treatment is to slow the rate of progression of fibrosis towards cirrhosis. For those with cirrhosis, it would be ideal if their already advanced degree of fibrosis could be reversed, to whatever extent. Although once thought irreversible, it is increasing recognized that cirrhosis can be reversed, to a greater or lesser extent.

Poynard et al (40) examined the impact of interferon treatment on liver histology. They pooled data from 3010 patients treated with various regimens of interferon, both standard and pegylated, in 4 randomized trials. 4493 patients were enrolled in the 4 trials but these 3010 patients had paired liver biopsies pre- and post-therapy (mean duration between biopsies 20 months). Interestingly, 75% of the patients had fibrosis stages of 0 or 1 and only 25% stages 2, 3 or 4, illustrating the selection bias of many such trials towards those with less advanced disease. Fibrosis stage improved in 20%, was stable in 65% and worsened in 15%. The activity (inflammatory) grade improved in 55%, was stable in 31% and worse in 14%. The rate of progression of fibrosis was reduced in comparison to rates before treatment. "Reversal" of cirrhosis was observed in 75 (49%) of the 153 patients with baseline cirrhosis. The cirrhosis regressed to stage 3 in 23 patients, to stage 2 in 26, to stage 1 in 23 and to stage 0 in 3.

Because of the many different treatment regimens and types of responses involved, conclusions according to regimen or response type were difficult to interpret. However, Peg-IFN plus ribavirin for 48 weeks showed the highest chance of fibrosis regression (24%) and the lowest for worsening (8%). Sustained virologic response was independently associated with regression of fibrosis from stage 2, 3 or 4 to stage 1 or 0. Further studies are needed that examine histologic changes after a much longer time, like 5 or 10 years, to see how durable changes in histology or rates of fibrosis really are, particularly in non-responders.

Summary

- **A negative HCV RNA value at 6 months post-end of therapy (SVR) is highly predictive of permanent loss of virus.**

- **Some patients, albeit a minority, show a reduction in fibrosis after treatment. This is more often seen in those with an SVR.**

Question 9 (part 2)
Q... my patient has failed treatment; now what?
A... depends on his stage of fibrosis and overall clinical status

NIH Consensus Development Conference statement
On further treatment of patients who have failed interferon monotherapy or Rebetron... "Knowledge of the severity of the underlying disease is important in recommending re-treatment. Patients with advanced fibrosis or cirrhosis should be considered for re-treatment."

*On further treatment of patients who have failed pegylated interferon and ribavirin... "Failure to respond to optimal therapy with pegylated interferon and ribavirin presents a significant problem. Until the results of (*currently*) ongoing studies are available, the role of long-term, continuous therapy with pegylated interferon should be considered experimental."*

Treatment decisions become more complicated once a patient has failed one treatment course. For those who have failed PEG-IFN & RBV, no further FDA-approved therapy is likely to be available for at least several years. Clinical trails are an option for some of these. For those who were non-responders to interferon monotherapy or to Rebetron, knowing the stage of fibrosis is an important aid in deciding about future treatment. Preliminary results (45) suggest that 25 to 40% of the former and 15% of the latter may achieve an SVR when treated with PEG-IFN + RBV. A number of re-treatment studies are ongoing, including those using a higher dose (3 ug/kg) of PEG-IFN alfa-2b.

Question 10
Q... what are the prospects for new treatment that might be more effective and/or easier?
A... nothing appears promising in the next 3 to 4 years, but many avenues of research are currently being pursued.

NIH Consensus Development Conference statement
On developing new therapies...
"Priority should be given to developing less toxic therapies and molecular-based agents that specifically inhibit viral replication and/or translation of viral RNA."

It appears that pegylated interferon and ribavirin will be the state-of-the-art treatment for at least the next several years, if not longer. At this time, there are no other drugs that are near FDA-approval. However, there are a number of avenues of research being pursued, not all related to direct viral eradication.

Some of the areas of research according to mechanism that are ongoing; in various stages of development from preclinical to phase III:

- *Inhibit progression of fibrosis*

... Long-term lower (50% of standard) dose Peg-interferon (HALT-C trial, COPILOT trial). Interferon alfa increases fibrinolysis, decreases collagen deposition and stabilizes hepatocyte membrane composition and, therefore, may inhibit progressive hepatic fibrosis independent of its antiviral effect. Gamma interferon and ribavirin monotherapy are also being examined for inhibition of progressive fibrosis.

- *Direct inhibitors of viral replication*

... Antisense oligonucletides can hybridize to viral RNA and thereby inhibit protein expression. Phase II trial in progress.
... Polymerase, helicase and protease inhibitors

- *Ribavirin analogues*

... Levovirin (L-isomer of ribavirin), viramidine (pro-drug of ribavirin)

- *IMPDH (rate-limiting enzyme for GTP synthesis) inhibitors*

... Mycophenolate mofetil (CellCept), VX-497

- *Immunomodulators*

... Synthetic thymosin, histamine dihydrochloride

- *Therapeutic vaccines*

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