APPLYING EVIDENCE TO THE CARE OF A PATIENT WITH HEPATITIS C: HOW TO DEVELOP A FOCUSED CLINICAL QUESTION

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Mr. Simon is a 45-year-old man with cirrhosis from chronic hepatitis C virus infection. The infection was diagnosed 5 years ago, when Mr. Simon presented with fatigue and was found to have abnormal liver tests. Further evaluation at that time revealed a viral load of 3 million copies per milliliter, a genotype of 1b, and mild inflammation and cirrhosis on liver biopsy. Since that time, Mr. Simon's cirrhosis has been compensated, with no ascites, encephalopathy, or variceal bleeding. He has never received treatment for chronic hepatitis C. He is currently being followed at a university-affiliated gastroenterology (GI) clinic.

At a recent GI appointment, Mr. Simon's gastroenterologist recommended that he begin combination therapy with pegylated interferon alfa and ribavirin. Mr. Simon was surprised and troubled by this recommendation and declined the treatment. It was his understanding that interferon alfa had severe side effects for all patients with chronic hepatitis C but was even more dangerous and less effective when the infection had advanced to cirrhosis. Mr. Simon reported that at the time of his diagnosis 5 years ago, his prior gastroenterologist had discussed the potential dangers of interferon alfa therapy and recommended that he not take it.

The current gastroenterologist explained that recent research found the treatment safe and effective in patients like Mr. Simon, who had compensated cirrhosis. Furthermore, the gastroenterologist said that if Mr. Simon responded to the treatment, he might avoid a liver transplant. Despite the promising new information, Mr. Simon remained very concerned about start-

ing treatment and said he wanted to think more about it and discuss it with you, his primary care physician.

You are a second-year resident who, for the past 2 years, has been seeing Mr. Simon at the university's primary care clinic. This morning, while seeing patients at the primary care clinic, you receive an e-mail from Mr. Simon's gastroenterologist alerting you about his interaction with Mr. Simon. You learn that Mr. Simon has an appointment to see you next week. How will you advise your patient?

Every day we confront a diverse and variable array of clinical questions we must navigate in the best interest of our patients. These questions can be particularly challenging in cases in which the underlying science is rapidly changing and the standard of care is a moving target. Many areas of medicine are evolving quickly, and the treatment of hepatitis C is clearly one of those areas. How can we be sure our patient care decisions are based on valid information when the scientific evidence is always changing?

Since it is not feasible to be knowledgeable about the most recent evidence in all clinical areas of our practice, we need skills that allow us to efficiently search for and apply appropriate evidence to our patient care decisions. Widespread recognition of this need has led to a growing trend toward practicing evidence-based medicine (EBM). Defined as the "integration of best research evidence with clinical expertise and patient values" [1], EBM is now regarded as an essential skill for physicians and is recognized by the Accreditation Council for Graduate Medical Education as a fundamental competency to be demonstrated by residents [2]. Incorporating best evidence into clinical care can be challenging, especially given the ongoing explosion of medical information. However, by using a systematic approach, physicians can develop and maintain the essential skills of evidence-based practice.

This issue of *Seminars in Medical Practice* initiates a new journal feature devoted to examining these

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important skills. The feature uses real patient cases to illustrate a five-step EBM approach that begins with an assessment of the patient-specific problem and progresses through the development of a focused clinical question, the search for evidence, the appraisal of evidence, and finally the application of evidence to patient care decisions (**Figure 1**). A key requirement of EBM is that it be efficient, so that it can be included as part of our busy practices. Thus, our goal is to teach the essential skills of EBM and to illustrate practical strategies for efficient use of these skills in routine decision making. We have chosen an article format that draws the reader into the process of applying best evidence to the care of the case patient, with a discussion of practical elements of the EBM process by "experts" who guide the reader at each step. We hope that this feature will be useful for residents and practicing physicians who wish to incorporate EBM into their decision making as well as for clinical educators who seek novel ways to teach these skills.

In this article, the reader is introduced to the five-step EBM approach and given practical instruction on how to develop a focused clinical question. As the patient scenario in this article illustrates, any patient encounter may give rise to many clinical questions. Deciding which question or questions to pursue and determining how best to find the answers are essential skills. This article explores important issues in developing and pursuing a common type of clinical question—a therapy question. Future articles will examine the specific skills involved in other steps in the EBM process.

Assessing the Clinical Problem

In anticipation of Mr. Simon's visit, you take time after clinic to review his medical record. Having cared for him for the past 2 years, you know him well. With hepatitis C cirrhosis, you are concerned about progression to liver failure and transplantation. Histories taken during recent visits suggested that Mr. Simon's cirrhosis was stable, and physical examinations revealed no evidence of ascites or encephalopathy. However, your notes remind you that much of Mr. Simon's last visit was spent addressing his debilitating fatigue and discussing his fear of liver failure. You recall your vague response when he asked how long until he would need a transplant. Because his liver disease has been evaluated at the GI clinic, the issue of treatment for his hepatitis C has not been raised during his visits with you. You now try to factor in the possibility of treatment to your own assessment of Mr. Simon.

You realize you are not familiar with the recent literature regarding treatment of chronic hepatitis C. As
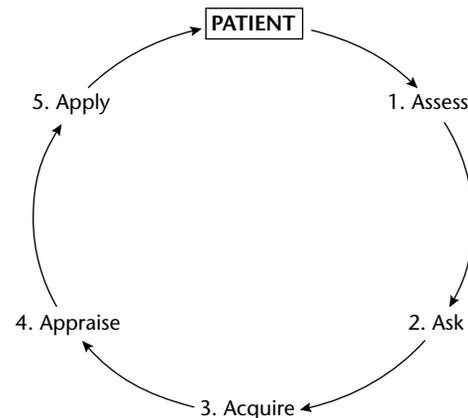

Figure 1. Five-step approach to applying current best evidence to patient care decisions. Evidence alone is never sufficient to direct decision making but must be combined with clinical expertise and put into context with patient values. First, we must *assess* the patient and problem to determine all information pertinent to patient care at that time. Next, we must draw from this information to *ask* a focused, patient-specific question. The next step is to efficiently *acquire* the needed evidence from an appropriate source. With an evidence source in hand, we then must *appraise* the evidence to further examine its validity and importance. Finally, we must consider the patient's unique values and circumstances to determine whether it is appropriate to *apply* the evidence to the care of the patient.

Mr. Simon's primary care physician, you want to address his concerns about treatment and help him understand how the most recent research findings might apply to him. Recognizing the need to expand your knowledge of the current standard of care for chronic hepatitis C, you decide to devote time to seeking current literature on this subject. Although your primary goal is to help Mr. Simon make the best decision regarding his care, you also are aware of the increasing prevalence of chronic hepatitis C and anticipate that your practice may soon include more patients with this disease.

Evidence-based practice begins with our thoughtful assessment of the patient problem at hand and our own learning needs. Evidence is most useful when applied in the appropriate context—matching our best assessment of patient needs and values with the best available information about the clinical problem when, where, and how we need it.

First, it is important that we gather accurate patient-specific information pertinent to the problem and the care decisions needed at that time (eg, historical data, physical examination findings, test results, patient concerns). A common fallacy is that EBM somehow devalues the fundamental tenets of the practice of medicine, specifically clinical expertise. A comprehensive understanding of

pathophysiology combined with a thorough clinical evaluation remain the critical starting point for the EBM process. Eliciting the patient's perspective on the problem is also critical to this first step, as patient values and concerns may ultimately drive the selection of questions to pursue and the discussion of how, if at all, evidence should be applied in the course of care.

Next, we must assess the urgency, timing, and magnitude of the clinical problem for our patient and consider whether future patients in our practice may face the same problem. Although we must ultimately decide whether to treat our patient for hepatitis C in order to avoid potentially life-threatening liver failure or transplantation, our current assessment reveals that he is clinically stable. Thus, we have time to pursue an evidence-based answer for Mr. Simon. In a time-critical situation, it may be quicker to accept at face value a specialist's approach to a particular patient, but in doing so we cannot be sure that the recommendation is based on valid evidence. Furthermore, if the problem is likely to affect future patients, we will want to pursue an evidence-based answer to guide our ongoing practice.

Then, we need to assess the state of the medical literature that will serve as the basis for our more targeted inquiry. Is this a new, evolving disease process that will require evolving information, or a question regarding an age-old problem, such as how to foster compliance with medications for hypertension?

Finally, we must ask: How up-to-date is our knowledge about the clinical problem? Practicing EBM means continually assessing our knowledge and deciding how to meet our individual learning needs.

Asking a Focused Clinical Question

As a first step in expanding your knowledge of hepatitis C treatment, you call Mr. Simon's gastroenterologist and are lucky to find him in his office. You ask if he could briefly explain his rationale for recommending combination therapy with pegylated interferon alfa and ribavirin and comment on Mr. Simon's concerns.

The gastroenterologist tells you that the toxicity issue involves interferon alfa, not ribavirin. He notes that 5 years ago there was not evidence to support the safety of interferon alfa in patients with hepatitis C cirrhosis. Thus, the standard of care was to not recommend treatment. However, he adds that data in the last few years have refuted these concerns, and treatment of cirrhotic patients with interferon alfa is common. He also tells you that a recent trial found that combination treatment with pegylated interferon alfa and ribavirin is the most effective therapy available, and this has become standard treatment in the GI clinic. He would

therefore not recommend unmodified interferon alfa or pegylated interferon alfa as monotherapy.

You thank the gastroenterologist for his time and helpful insights. With this information you can now frame a search for recent literature to help you prepare for your discussion with Mr. Simon. Keeping in mind your patient's concerns, you jot down your learning issues relevant to treating chronic hepatitis C: 1) safety of interferon-based therapy and 2) effectiveness of combination therapy with pegylated interferon alfa and ribavirin. You use these issues to map out a focused clinical question and sit down at a clinic computer to begin an online search of the literature.

Once we are satisfied we have assessed the patient and problem, the next step is to draw from our assessment one or two issues relevant to the patient's care and convert those issues into clinical questions. In this step, we are identifying a need for further information on which to base a care decision and framing that needed information as a focused, patient-specific question. Despite its critical importance in the EBM process, question development is not emphasized in most clinical training programs. In a recent survey of 417 internal medicine residency program directors, only 44% of programs with EBM curricula included posing a focused question as an objective [3].

Background versus Foreground Questions

Like most patient cases, this case raises a wide range of questions that might be pursued. Generally, clinical questions can be conceptually divided into two main types. *Background questions* ask for general knowledge about biologic or other fundamental aspects of an illness, whereas *foreground questions* ask for specific knowledge about managing certain aspects of the care of a patient with a specific condition [4]. Generally, as clinical experience with managing specific disorders increases, questions change from being primarily background questions to being mainly foreground questions. For example, a medical student, who has little clinical expertise and knowledge needed to care for a patient with hepatitis C, might ask the following (background) questions regarding the pathophysiology of Mr. Simon's condition:

- How does hepatitis C cause cirrhosis?

- How can I be sure this patient has cirrhosis?

- What is the difference between compensated and decompensated cirrhosis?

- What are the clinical features of decompensated cirrhosis, and how do they develop?

A more experienced clinician, who is already familiar with the pathophysiology of compensated cirrhosis,

Table 1. Examples of Foreground Questions Related to the Care of Mr. Simon

Central Issue	Question(s)
Therapy	Is therapy with interferon alfa and ribavirin more effective than interferon alfa monotherapy?
	Is pegylated interferon alfa more effective than unmodified interferon alfa?
	Is ribavirin necessary, or is pegylated interferon alfa alone effective?
Harm	What are the side effects of treatment with interferon alfa?
	What are the side effects of treatment with ribavirin?
	Do the side effects occur in all patients?
Prognosis	What is the likelihood that he will develop encephalopathy?
	What is the impact of alcohol on the risk of cirrhosis in patients with hepatitis C?
	How many patients die before receiving a liver transplant?
	What survival rate is associated with liver transplants for hepatitis C?
	What happens to hepatitis C after transplant?
Diagnosis	Is liver biopsy a reliable diagnostic tool for cirrhosis?
Economic analysis	Is treatment of hepatitis C cost-effective?

might ask targeted questions about an array of issues relevant to the best care of Mr. Simon (**Table 1**). For example, (foreground) questions specifically about treatment might include:

- Is therapy with interferon alfa and ribavirin more effective than interferon alfa monotherapy?

- Is pegylated interferon alfa more effective than unmodified interferon alfa?

- Is ribavirin necessary, or is pegylated interferon alfa alone effective?

Regardless of our level of training, the list of questions we might generate about a given patient can be overwhelming. It is neither practical nor desirable to pursue all questions with equal fervor. If we are to pursue clinical questions throughout our careers, we must learn to do this efficiently. Scarcity of time for self-directed learning and limited resources require that we prioritize our questions. In fact, all questions are not created equally—some will have a greater or more immediate impact on patient care and simply must be considered first. After surveying all interesting and pertinent questions raised, we should consider the following: 1) Which question is most relevant to the care of the patient and is feasible to answer within the time available? 2) Which question is most likely to come up again, in the care of other patients? We cannot form effective foreground questions without a certain foundation of clinical expertise. From a trainee's point of view, when you find yourself in a clinical area in which

you have less experience, the assistance of a background reading source, supervising faculty member, or consultant can be invaluable in clarifying the important issues.

Anatomy of a Focused Clinical Question

In our assessment of Mr. Simon's case, we recognized that he is especially worried about the safety of interferon alfa but also wants assurance that the recommended treatment would be beneficial. Thus, our two identified issues important to helping Mr. Simon decide whether to begin therapy might be converted to the following questions:

- Is treatment with interferon-based therapy safe?

- Is combination therapy with pegylated interferon alfa and ribavirin effective?

To ensure we get answers that apply to Mr. Simon, we need to focus our questions with more detail so we can efficiently and effectively use the resources of the medical literature. One useful approach is to frame our clinical questions using the PICO components defined in **Table 2**. In this framework, most questions have four components: the patient, population, or problem of interest (P); the main intervention, exposure, or prognostic factor being considered (I); the comparison, if applicable (C); and the outcome of interest (O) [5]. A question in PICO format can drive the rest of the EBM process and help to identify search terms.

It is useful to note that we have two separate questions concerning therapy: one on harm and one on effectiveness.

Table 2. Essential Components of a Focused Clinical Question (PICO)

P = Patient, population, or problem (How would I describe a group of patients similar to mine?)

I = Intervention, exposure, or prognostic factor (Which main intervention, exposure, or prognostic factor am I considering?)

C = Comparison (What is the main alternative to compare with the intervention, exposure, or prognostic factor?)

O = Outcome (What can I hope to accomplish, measure, improve, or affect?)

This distinction is important, because we may find answers in different sources. At this point, however, we do not have an adequately defined patient, population, or problem. Based on information from the GI consultant, interferon alfa is a well-established treatment for hepatitis C. Mr. Simon raised the issue that his cirrhosis was previously considered a contraindication to therapy. Therefore, our questions might be better stated:

- In patients with **hepatitis C and cirrhosis,** is treatment with interferon-based therapy **safe**?

- In patients with **hepatitis C and cirrhosis,** is treatment with pegylated interferon alfa and ribavirin **effective**?

Next, we need to define the intervention and comparison components of our questions. The GI consultant indicated that combination therapy with pegylated interferon alfa and ribavirin is the current standard of care for treatment of hepatitis C. As for a comparison intervention, the gastroenterologist does not recommend any other treatment, although other options do exist. Mr. Simon has clearly stated his concerns about interferon-based treatment. With the input of the patient and the consultant, our questions now are:

- In patients with **hepatitis C and cirrhosis,** is treatment with **pegylated interferon alfa and ribavirin**, compared with no treatment, **safe**?

- In patients with **hepatitis C and cirrhosis,** is treatment with **pegylated interferon alfa and ribavirin**, compared with no treatment, **effective**?

Finally, we need to define the outcome component of our questions. Review of the hepatitis C literature shows that the commonly stated outcome of treatment is the

Table 3. Examples of Clinical Questions Relevant to the Care of Mr. Simon, in PICO Format

Question

In patients with hepatitis C and cirrhosis, is treatment with pegylated interferon alfa plus ribavirin more effective than treatment with unmodified interferon alfa?

In patients with hepatitis C and cirrhosis, what are the side effects of treatment with pegylated interferon alfa and ribavirin?

What is the likelihood that a patient with untreated hepatitis C and cirrhosis will develop decompensated cirrhosis?

In patients with hepatitis C, is liver biopsy a reliable diagnostic tool for cirrhosis?

In patients with hepatitis C and cirrhosis, is treatment with pegylated interferon alfa and ribavirin cost-effective?

sustained virologic response (SVR), which means the patient has no evidence of hepatitis C RNA 6 months after completing therapy. Although we may prefer other outcome measures, such as quality of life, mortality, or progression to liver transplantation, information on these measures is currently lacking in the hepatitis C literature. Thus, our final, focused questions are:

- In patients with **hepatitis C and cirrhosis,** is treatment with **pegylated interferon alfa and ribavirin,** compared with **no treatment, safe**?

- In patients with **hepatitis C and cirrhosis,** how often does treatment with **pegylated interferon alfa and ribavirin,** compared with **no treatment,** lead to a **sustained virologic response**?

The question-building process is a skill that can and should be applied to all clinical questions that arise in the course of patient care. **Table 3** examines several questions relevant to Mr. Simon's case and outlines the pertinent (PICO) components.

Acquiring the Current Best Evidence

You are familiar with the online resources available through the university and decide to try the filtered evidence databases first. You begin your search by accessing the Cochrane Database of Systematic Reviews. A search on the term "interferon" produces 53 hits; a search on "hepatitis" results in 46 citations. Combining these terms, you get 17 hits. Scanning the titles you

Patient, Population, or Problem	Intervention, Exposure, or Prognostic Factor	Comparison	Outcome	Type of Clinical Question
Hepatitis C, Cirrhosis	Pegylated interferon alfa and ribavirin	Unmodified interferon alfa	Sustained virologic response	Therapy
Hepatitis C, Cirrhosis	Pegylated interferon alfa and ribavirin	No treatment	Adverse events and toxicity	Harm
Hepatitis C, Cirrhosis	Time		Development of decompensated cirrhosis	Prognosis
Hepatitis C	Liver biopsy	Autopsy	Cirrhosis	Diagnosis
Hepatitis C, Cirrhosis	Pegylated interferon alfa and ribavirin	No treatment	Quality adjusted life years	Economic analysis (back to Question)

find a systematic review from 1999 titled "Interferon for interferon naive patients with chronic hepatitis C" [6]. Within minutes from the start of your search, you see the summarized results of 54 trials enrolling 6545 patients, including patients with cirrhosis. Quickly scanning this review, you note that it does not include trials with pegylated interferon alfa. However, it appears to address components of your questions, so you print it to read later.

You then turn to the online version of *ACP Journal Club* to search for newer evidence in the form of an abstracted research study. A search of "hepatitis C" yields 12 citations in under 1 minute, the first of which is titled "High-dose peginterferon α-2a sustained virologic and biochemical response in chronic hepatitis C infection with cirrhosis" [7]. This study summary indicates that pegylated interferon alfa decreased viral load and was safe in patients with hepatitis C and cirrhosis. It also states that the study was the largest trial to date of antiviral therapy in patients with cirrhosis and hepatitis C infection. You print this useful summary to review again later.

After skimming the evidence found thus far, you feel better about the safety and effectiveness of interferon-based therapy for Mr. Simon, but your search has not revealed any evidence regarding combination therapy with pegylated interferon alfa and ribavirin. You then turn to MEDLINE to search for original research studies that address the elements of your clinical question. Entering the Medical Subject Heading (MeSH) terms for the patient population (hepatitis C) and intervention

(Interferon-alpha, Ribavirin, and Combination Drug Therapy) and searching specifically for randomized controlled trials, you narrow the field to 56 articles (**Figure 2**). Scanning the titles, you spot a very promising article from the *Lancet*, titled "Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C: a randomised trial" [8]. Although you were able to find this study in less than 15 minutes, you are out of time. You print the full text of the article, which is available online, and take it home to read tonight.

Armed with our focused clinical questions, our attention next turns to searching the medical literature for evidence to answer our questions. Many evidence-based information sources are currently available for online searching. These sources vary in their ease of use, reliability for answering specific types of questions, and value for addressing questions as they arise in practice. Appreciating the pros and cons of each type of information source helps in determining when each can best be applied. For example, a referenced textbook would be an appropriate first step in the search for answers to a medical student's questions regarding the pathophysiology of cirrhosis and the development of encephalopathy. However, a textbook is unlikely to help answer our questions about new treatments for chronic hepatitis C, as new advances often are not found due to the typically long time between the writing and publishing or updating of textbooks. Considering the recent introduction of combination therapy with pegylated interferon alfa and ribavirin, we need to

#	Search History:	Results
1	Exp *Hepatitis C/	17937
2	Exp *Interferon-alpha/	10609
3	*Ribavirin/	2019
4	1 and 2 and 3	470
5	Drug Therapy, Combination	67792
6	4 and 5	324
7	Randomized Controlled Trial.pt	162951
8	6 and 7	56

Figure 2. Search history from OVID: MEDLINE Database 1966 to July Week 1 2002. The *explode* (exp) function allows you to include more specific and relevant terms in your search strategy by automatically including the broad term and all related terms indented under it (eg, for hepatitis C, this term would encompass hepatitis C and chronic hepatitis C). The *focus* (*) function indicates that the Medical Subject Heading (MeSH) term is the primary focus of the article; its use can result in a more relevant retrieval. The *publication type* (pt) feature allows you to limit your search to specific types of articles (eg, trials, reviews).

seek data from clinical trials to answer our questions regarding the safety and effectiveness of this regimen.

Filtered versus Unfiltered Evidence Sources

We cannot expect to review and assess every important clinical trial that is published, so if we devote ourselves to evidence-based practice, we need to be efficient in our efforts to search for appropriate evidence that is in the best interest of our patients. One useful strategy is to take advantage of *filtered* evidence sources, such as databases of systematic reviews or evidence-based journal abstracts. These resources save valuable time because the information selected for inclusion in the database has been prescreened for validity and clinical importance. In a well-done systematic review, the authors comprehensively collect, appraise, and summarize all the relevant published and unpublished research studies for a focused clinical question. An evidence-based journal abstract examines one individual study, screens for validity, and comments on clinical relevance. If the clinical question is not addressed by one of these resources, we may need to turn to an *unfiltered* source, such as MEDLINE, which can provide direct access to research studies. Some pros and cons of the evidence sources accessed in our search are shown in **Table 4**.

With a focused clinical question and a basic knowledge of the available sources of evidence, we should be able to search the medical literature efficiently. For example, our search of filtered evidence databases (ie, the Cochrane Database of Systematic Reviews, *ACP Journal Club*) took less than 10 minutes in total to produce helpful information relevant to our patient's concerns. Although more involved, our MEDLINE search took less than 15 minutes to produce a highly relevant study using search terms taken directly from the PICO question format. Taking the time to clearly focus our clinical question helps build an effective search strategy and makes searching more efficient.

Appraising Evidence for Validity and Importance

Later that evening you review the information downloaded from your search. Your goal is to assess whether the evidence is valid and helpful for informing your discussion with Mr. Simon. You have a working knowledge of the critical appraisal process and are happy that some of the evidence has been appraised for you.

The systematic review states that unmodified interferon alfa is effective in clearing virus in patients with chronic hepatitis C and that interferon alfa is safe and associated with similar benefits in patients with cirrhosis. The placebo-controlled trials summarized in this review helped to establish interferon therapy as the standard of care for hepatitis C. This report summarizes the literature only through 1999, however. It does not include information on pegylated interferon alfa or combination therapy with ribavirin, and it does not address toxicity in patients with cirrhosis.

The abstracted study summary states that pegylated interferon alfa monotherapy was more effective than unmodified interferon alfa for eradicating virus in patients with cirrhosis from hepatitis C. This study also found similar rates of adverse events in each group of patients. Given that most of the morbidity of hepatitis C therapy is due to the interferon alfa, this study is helpful in addressing Mr. Simon's safety concerns. However, the summary authors note that standard treatment is interferon alfa and ribavirin; thus, the authors conclude that they cannot not make a final recommendation for pegylated interferon alfa monotherapy.

You pause to ponder what you have just read. You have found evidence that combination therapy (unmodified interferon alfa plus ribavirin) is effective in patients with cirrhosis and evidence that this combination is safe. However, you still have not seen evidence regarding combination therapy with pegylated interferon alfa and ribavirin. By this point, your interest is piqued so you decide to go further.

You turn your attention to the original research study found on MEDLINE. Using the criteria you know are important for critical appraisal (**Table 5**), you note

Table 4. Evidence Sources Used in This Case: Pros and Cons

Pros	Cons
Cochrane Database of Systematic Reviews (systematic reviews, meta-analyses)	
Focuses on interventions	Small database, not comprehensive
Easy to search	Reviews can be cumbersome to read
Searches across several databases	
Searches by text words or subject heading	
***ACP Journal Club* (enhanced abstracts of selected original research studies)**	
Studies meet validity criteria	Small database; updated only 6 times per year
Abstract provides bottom-line information	Focuses on internal medicine topics
Expert commentary puts study into context of current research	Identifies individual studies (may not represent full scope of literature on the subject)
MEDLINE (bibliographic database of original research studies)	
Comprehensive	Can require detailed search strategy
Indexed with standard terminology	Not filtered; articles require critical appraisal
Updated daily (PubMed)	
Free (PubMed)	

that this was a randomized (allocation concealed), blinded (outcome assessors), and controlled study to determine whether pegylated interferon alfa and ribavirin is more effective than unmodified interferon alfa and ribavirin in patients with hepatitis C. All patients had chronic infection and had never been treated; 28% to 30% of patients in each treatment group had bridging fibrosis or cirrhosis. Patients with decompensated cirrhosis were excluded. At baseline, patients in the control group were similar to those in the study groups. Follow-up was complete. Although patients and providers were not blinded, you are satisfied that most other important elements of valid study design were attended to, so you carry on.

You note that therapy with high-dose pegylated interferon alfa plus ribavirin was more effective than therapy with unmodified interferon alfa plus ribavirin. SVR rates were 274/511 (54%) in the high-dose pegylated interferon alfa group and 235/505 (47%) in the unmodified interferon alfa group ($P < 0.001$). You remember that the Number Needed to Treat (NNT) can be calculated easily by taking the reciprocal of the Absolute Risk Difference (ARD). You quickly do this calculation (ARD: $0.54 - 0.47 = 0.07$; NNT= $1/0.07 = 14.28 \rightarrow 15$). You know that an NNT of 15 is quite good and feel that this evidence does support the use of combination therapy with pegylated interferon alfa and ribavirin in Mr. Simon. You also note that side effect profiles were similar for the two treatments in patients with and without cirrhosis.

Our initial attempts at an efficient search using filtered sources yielded two pieces of evidence helpful in addressing the safety and effectiveness of interferon-based therapy, but we had to search MEDLINE to find evidence addressing combination therapy. Our next step is to critically appraise the evidence for its validity and clinical importance. Because the systematic review and abstracted study have been preappraised for validity, we can proceed to the original research study examining combination therapy with pegylated interferon alfa and ribavirin. In this case, the onus is on us to decide whether the evidence from the study is valid and important. Criteria to guide this assessment are well established, with one example shown in Table 5. After considering each of the questions for appraising the validity of a therapy study, we have concluded that the results of the study from the *Lancet* [8] are, indeed, valid.

In deciding whether the results of the study should impact Mr. Simon's care, we must consider the outcomes being measured. The study suggests that if we treat 15 patients like Mr. Simon with pegylated interferon alfa plus ribavirin, we will gain one additional virologic response as compared with therapy with unmodified interferon alfa plus ribavirin (NNT = 15). This difference does reach statistical significance; however, it is up to us to decide whether this is a clinically important effect. Ideally, we would measure progression to liver transplantation, mortality, and quality of life to guide our treatment decision for Mr. Simon.

Table 5. Criteria for Appraising and Applying an Individual Therapy Study

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Are the results valid?

Did experimental and control groups begin the study with a similar prognosis?

- Were patients randomized?
- Was randomization concealed (blinded or masked)?
- Were patients analyzed in the groups to which they were randomized?
- Were patients in the treatment and control groups similar with respect to known prognostic factors?

Did experimental and control groups retain a similar prognosis after the study started?

- Were patients aware of group allocation?
- Were clinicians aware of group allocation?
- Were outcome assessors aware of group allocation?
- Was follow-up complete?

What are the results?

- How large was the treatment effect?
- How precise was the estimate of the treatment effect?

How can I apply the results to patient care?

- Were the study patients similar to my patient?
- Were all clinically important outcomes considered?
- Are the likely treatment benefits worth the potential harm and costs?

Adapted with permission from Guyatt G, Rennie D. Users' guides to the medical literature. Chicago: AMA Press; 2002:58.

However, for hepatitis C, like other diseases with slow disease progression (over decades), these outcomes are difficult to measure, leaving us with the secondary outcome of clearance of viral load (SVR). Given our current understanding of the pathophysiology of hepatitis C, we do believe that a SVR will translate into improved clinical outcomes for our patient.

Applying Evidence to Patient Care

You now return to Mr. Simon's case to reassure yourself that these data are relevant to him. In fact, all three studies did include large numbers of patients similar to Mr. Simon (ie, with compensated cirrhosis). The results of these trials convince you that the risks of interferon-based therapy are similar in patients with and without cirrhosis. In addition, you are encouraged that the proposed regimen (ie, pegylated interferon alfa-2b and ribavirin) is the most effective available therapy and can produce a SVR in more than half of patients, including those with compensated cirrhosis. You now feel equipped to present these findings to Mr. Simon and to help him consider the pros and cons of treatment.

At your visit with Mr. Simon, you first establish that his liver disease remains stable, with no signs of decompensated cirrhosis. You then acknowledge his concerns about the therapy recommendation he was given in the GI clinic. In summarizing the relevant literature for him, you explain that you have just carefully reviewed a series of scientific studies addressing the question of whether or not interferon alfa was safe in patients like him. You note that these studies showed there were side effects of treatment in all patients, but the side effects were no worse and no more dangerous in patients with liver disease just like his (compensated cirrhosis). In addition, you note that you found a large study from last year that shows the newer therapy (pegylated interferon alfa-2b and ribavirin) is more effective at clearing virus than the treatment that was available 5 years ago.

Mr. Simon is surprised to learn that patients with compensated cirrhosis had been included in research studies for some time. He says this information about interferon being safe for someone like him is completely new to him, as is the information about improved response rates with the latest treatment. He admits that he was so shaken by the suggestion of treatment in the GI clinic, he did not recall any of the numbers the gastroenterologist quoted him.

Mr. Simon adds that he does read about hepatitis C on the Internet and has found that some people report severe side effects with treatment. Returning to the fatigue he has previously described, he says he is concerned he cannot tolerate medications that will only make him feel worse. You acknowledge that treatment can be extremely difficult to tolerate for some patients. You try to reassure him with strategies to help with side effect management and remind him that he will have the option of stopping treatment if the side effects are debilitating. However, you emphasize again that you feel the new treatment offers him the best opportunity to avoid a liver transplant. Mr. Simon tells you he would like to think things over with his family and contact you next week. You reassure him that you are available for him as he comes to terms with this decision.

Having judged our evidence to be both valid and important, our final task is to determine whether the evidence applies to our patient and whether it is helpful in guiding a decision. Every management decision requires deliberation and judgment that take into consideration not only the evidence found, but also the unique viewpoints, values, and experience of the patient.

Certain questions can guide our thoughts when trying to apply evidence from a therapy study to an individual patient (*see* Table 5). In the case of Mr. Simon, all studies we found included patients who appeared very similar to him (ie, with hepatitis C compensated cirrhosis). Each piece of evidence added something to our understanding of Mr. Simon's particular situation. We next must consider whether the treatments or interventions are comparable. In this case, partly due to the rapidly evolving standard of care for treatment of chronic hepatitis C, each study looked at a different set of interventions: The systematic review compared unmodified interferon alfa to placebo, the abstracted study looked at pegylated interferon alfa compared to unmodified interferon alfa, and the original research study compared combination therapy with pegylated interferon alfa and ribavirin to combination therapy with unmodified interferon alfa and ribavirin. For Mr. Simon, our only reasonable choices are the standard of care (pegylated interferon alfa plus ribavirin) or no treatment. However, we are not likely to find a clinical trial comparing those groups, as it may not be ethical to study that comparison in 2002. In this circumstance, we are obliged to generalize the study results as they represent the best evidence available for this clinical question. It is not unreasonable to individualize the results of the three pieces of evidence to Mr. Simon's circumstance and to conclude that the standard of care combination therapy is the safest and most effective option available to him.

Once satisfied that the evidence does apply to our patient, the final challenge is to combine the evidence with our clinical expertise and compassion for our patient. In trying to engage best available evidence in the best interest of our patients, we must take the information from the medical literature and try to communicate the bottom-line to our patients within the context of their own values and preferences. Potentially relevant issues in making a therapy decision include patient quality of life on treatment, impact of treatment on the patient's family, and religious or cultural beliefs. Costs of therapy and access to resources may also play a role when making a decision regarding treatment. With our help, each patient ultimately must determine the importance of these various factors.

This case specifically highlights the need to involve patients in the process of applying evidence to care decisions. Although it may be the best evidence, a randomized controlled trial has little meaning if it is inconsistent with the goals, values, and beliefs of the patient. In this case, our educated patient has been caught in the middle of a transition in the standard of care. Mr. Simon is asking insightful questions based on a previous physician's advice regarding the potential serious side effects and lack of effectiveness of interferon therapy. In this case, Mr. Simon had placed all of his trust in the recommendation of his previous physician. At the time that this advice was given, it did reflect best available evidence. Emerging treatment choices and additional follow up in patients with cirrhosis, however, gives us new, best-available evidence in 2002. Mr. Simon was also influenced by the information he found on the Internet regarding side effects of therapy. As our patients become more aware and savvy about the resources available on the Internet and in the medical literature, we need to be prepared to address their questions and concerns. Through this process, Mr. Simon listened, voiced understanding, and left trying to determine his next course of action.

It is our obligation as Mr. Simon's current physicians to keep up with evolving therapies and improvements in the standard of care. We must be able to find, interpret, and ultimately apply the evidence that can direct our recommendation as to whether Mr. Simon should consider initiating therapy with a regimen that previously was not available to him. Then, in a setting of trust and mutual respect, together with Mr. Simon we can make the final decision.

Conclusion

Table 6 summarizes the five-step EBM approach as it applies to Mr. Simon's decision whether or not to proceed with a new treatment regimen for his chronic hepatitis C. This case highlights many of the challenges of modern clinical practice. Medical information is expanding and, in some cases, changing very rapidly. We are in the midst of a boom in new drug development. We have patients who are more educated and who want to take a more active role in their health care. These new developments can positively affect our practice and the care we provide. EBM offers an effective strategy for searching, evaluating, and incorporating information from the medical literature into our clinical care. By taking advantage of technological advances and resources such as systematic reviews and evidence-based journal abstracts, EBM can be efficient and used at the point of care. In this way, we ultimately can deliver what our patients deserve—thoughtful, considerate care guided by the best evidence.

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Table 6. Summary of the Evidence-Based Approach to Therapy Decisions for Mr. Simon

Assess	
The patient	Mr. Simon has compensated hepatitis C–related cirrhosis and must reassess prior recommendations regarding treatment. Specifically, the original decision to avoid interferon alfa based on concerns about efficacy and safety in patients with cirrhosis is called into question. You and Mr. Simon are confronted with a change in the standard of care based on new evidence. How should you best advise him?
The problem	The GI consultant clarifies that the question of potential harm should focus on interferon alfa, not ribavirin. However, the current standard of care for treatment of hepatitis C involves pegylated interferon alfa in combination with ribavirin. Thus, to address the therapy question, you should consider the combination.
Ask	1. In patients with hepatitis C and cirrhosis, is treatment with pegylated interferon alfa and ribavirin, compared with no treatment, safe?
	2. In patients with hepatitis C and cirrhosis, how often does treatment with pegylated interferon alfa and ribavirin, compared with no treatment, lead to a sustained virologic response?
Acquire	Systematic review from the Cochrane Library (< 5 minutes to obtain)
	Abstracted research study from *ACP Journal Club* (< 5 minutes to obtain)
	Original randomized controlled trial (RCT) from MEDLINE (< 15 minutes to obtain)
Appraise	<u>Systematic review</u>. Review indicates unmodified interferon alfa is effective in patients with chronic hepatitis C; also states that interferon alfa is safe and associated with similar benefits in patients with cirrhosis. No comment on pegylated interferon alfa.
	<u>Abstracted research study</u>. Summary indicates that treatment with pegylated interferon alfa-2a is safe in patients with hepatitis C cirrhosis and also decreases viral load. (Time: 15 minutes to read and ponder. Article is preappraised; therefore, validity screen is done for you.)
	<u>RCT</u>. This study of patients with compensated cirrhosis indicates that pegylated interferon alfa combined with ribavirin is safe and effective. (Time: 1 hour to read and ponder. Article is not preappraised; therefore, you must critique and digest the material on your own.)
Apply	Valid evidence suggests that patients with hepatitis C cirrhosis can benefit from treatment with pegylated interferon alfa and ribavirin. Although not more toxic in patients with compensated cirrhosis, the therapy has significant side effects. Therefore, the decision to treat a patient must include consideration of how the patient views the potential benefits and risks (eg, toxicities) of therapy. For Mr. Simon, the ultimate decision on treatment hinges on how he will weigh these factors.

References

1. Sackett DL, Strauss SE, Richardson WS, et al. Evidence-based medicine. How to practice and teach EBM. 2nd edition. London: Churchill Livingstone; 2000.
2. Accreditation Council for Graduate Medical Education. Outcome project: enhancing residency education through outcomes assessment. Competency language (full version). Available at http://www.acgme.org/outcome/comp/compFull.asp. Accessed 7 May 2002.
3. Green ML. Evidence-based medicine training in internal medicine residency training programs. J Gen Intern Med 2000;15:129–33.
4. Guyatt G, Rennie D. Users' guides to the medical literature. Chicago: AMA Press; 2002.
5. Richardson WS, Wilson MC, Nishikawa J, Hayward RSA. The well-built clinical question: a key to evidence-based decisions [editorial]. ACP J Club 1995 Nov-Dec;123:A12.
6. Myers RP, Regimbeau C, Thevenot T, et al. Interferon for interferon naive patients with chronic hepatitis C (Cochrane Review). Cochrane Database Sys Rev 2002;(2):CD000370.
7. Shehab T, Schoenfeld P. Commentary on "High-dose peginterferon α-2a sustained virologic and biochemical response in chronic hepatitis C infection with cirrhosis. ACP J Club 2001 Sept–Oct;135:52. Comment on: Heathcote EJ, Shiffman ML, Cooksley WG, et al. Peginterferon alfa-2a in patients with chronic hepatitis C and cirrhosis. N Engl J Med 2000;343:1673–80.
8. Manns MP, McHutchison JG, Gordon SC, et al. Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C: a randomised trial. Lancet 2001;358:958–65.