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MANAGING THE SIDE EFFECTS OF HEPATITIS C TREATMENT IN A CORRECTIONAL ENVIRONMENT

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Introduction:

The side effects of therapy of hepatitis C virus (HCV) infection have limited the number of patients able to complete an effective course of treatment and can dissuade patients and clinicians from embarking on such treatment. This is true in the general population as well as the more controlled correctional environment. Rates of discontinuation of HCV therapy for laboratory abnormalities or other clinical adverse events range from 7 to 16% in both HCV treatment trials and clinical practice.[1,2]

At the Hawaii Department of Public Safety, we have implemented a successful HCV treatment program for infected inmates. Although treatment began for a few inmates as early as 1999, the main emphasis on treatment started in late 2002. Approximately 6,000 inmates reside in Hawaii's prisons and jails, both of which are contained in one system. Inmates reside in eight facilities on four islands in Hawaii and in four private contract facilities in four different mainland states. The prevalence of HCV in our system in 1999-2001 was found to be approximately 30% when our health department tested all inmates anonymously. Although testing for HIV is routinely offered to inmates by our health department, screening for HCV is conducted when an abnormal ALT is detected or there is a history of injection drug use, transfusions before 1992, known liver disease, HIV infection or hepatitis B virus (HBV) infection. In addition, HCV testing is offered to patients on hemodialysis and prior to treatment with either isoniazid or statins, or on patient request. After determining HCV seropositivity, our current major criteria for consideration for HCV treatment is an ALT greater than 1.5 times normal (we previously used twice normal, but as the literature suggests a small percent of persons with progressive disease may have minimal or no elevation of ALT, we reduced this level to 1.5 times normal). Viral load and genotyping are then done to determine duration of treatment required and the need for liver biopsy. At the current time, we only perform liver biopsies on HCV genotypes 1 and 4. We do not treat fibrosis level 0 or 1, although we have made rare exceptions.

Our guidelines currently require an expectation for 12-18 months remaining in one's sentence, but exceptions are made for those committed to treatment and able to name an outside provider who will continue treatment. We previously required completion of or current participation in a drug treatment program but we have dropped that requirement for legal considerations. We do require sobriety and conduct random urine drug screens (after a signed agreement from the patient).

In analyzing our clinical data, we noted that only 5% of 188 patients treated for HCV had discontinued HCV therapy for medical reasons and 2% stopped treatment on their own for reasons that may or may not have been related to side effects. An additional 4% had their HCV therapy stopped secondary to positive urine drug screens. No patient has had a positive drug screen since November 2002. All inmates are tested for HIV prior to treatment; only three inmates of our treated population were co-infected.

While we suspect our approach to the management of treatment is similar to that of most providers, our ability to recognize and respond to HCV treatment-related toxicities is likely a significant factor contributing to the success we have had in achieving treatment completion. In this review we describe our approach to the management of the side effects we commonly encounter during HCV therapy.

General approach to treatment

We aim to assign a nurse at each facility to take responsibility for HCV management and also get the active participation of the nurse administrator. The overall management of HCV from diagnosis, evaluation and consideration of liver biopsy, explanation of the rationale for decisions not to treat (e.g., liver biopsy with fibrosis 0-1), to supportive care during treatment, all require the

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LETTER FROM THE EDITOR

Dear Corrections Colleagues,

At least 3 million people in the United States live with chronic Hepatitis C Virus (HCV) infection and many are involved in the criminal justice system. In several areas of the country, the prevalence of HCV in prisons and jails exceeds 30% and in some prisons almost half of the inmates are reportedly infected. The actual prevalence of HCV among inmates is certainly higher as screening for HCV in correctional facilities is not universal.

The establishment of standards of care for HCV management, which include the use of expensive therapies, has led to an increased demand for HCV treatment among inmates but has strained prison and jail health care budgets. While different facilities have adopted disparate and individualized approaches to the financing of HCV therapy, the medical management of this infection in our correctional system should be much less variable. As detailed in IDCR (October, 2005, July 2005), guidelines for the diagnosis and treatment of HCV have been established and include recommendations made by the National Institutes of Health (NIH) and the American Association for the Study of Liver Disease (AASLD) among others.

However, applying these recommendations to corrections has not always been straightforward and among the arguments for the deferral of HCV therapy during incarceration the cost of treatment is often accompanied by concerns regarding its tolerability. In this issue, Drs. Bauman and DeWitt from the Hawaii Department of Public Safety share their experience in managing the complications of HCV therapy and describe the underpinnings of their impressive rate of HCV treatment completion. Their success should be reassuring to correctional clinicians considering implementing HCV treatment programs. Their report is complemented by a series of insightful case discussions by Dr. Douglas Fish of the Albany Medical College. Later this year, Dr. David Paar will report in IDCR on the evolution of the Texas Department of Corrections' policies on the diagnosis and management of HCV.

The experience of these clinicians and those from other correctional systems make it increasingly difficult to reasonably justify the denial of HCV therapy to inmates who medically qualify for therapy and who will be incarcerated for a sufficient duration of time to receive treatment.

Sincerely,

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MANAGING THE SIDE EFFECTS...
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involvement of a consistent team of nurses and other providers. Most clinical visits (frequently timed with lab draws) are with the nurse on the treatment team. He or she assesses whether or not additional physician visits are also needed.

Patient expectations play a major role in the subjective patient response to side effects. During counseling, we stress the potential benefits of the current treatment and use the term "chemotherapy" to describe the treatment course itself. Some believe this is too strong a term, but our experience supports using this term, as it better predicts for the patient the severity of the side effects. We believe forewarned is fore-armed. We explain the 60/40 "odds" of achieving a sustained viral response (SVR; non-detectable virus at 6 months post treatment) or "cure" for HIV-uninfected patients with genotype 1 HCV, but also the potential reduction in liver inflammation and the resultant delay in the complications from chronic HCV even in the absence of SVR.[3] This we describe to the patient as "turning the clock back" on this disease.

Common side effects

Fatigue, headache, malaise, myalgias, arthralgias This combination of symptoms leads any list of HCV treatment side effects and is reported to occur in over 50% of treated patients; in some studies this proportion is as high as 72%.[1-6] Most patients experience these symptoms to some degree. Liberal prescribing of analgesics may help with the aches. Further, we administer pegylated interferon injections on late afternoons on Fridays so patients have the weekend to recover. By Monday, they are usually able to tackle work once again. Rarely have our patients had to leave their work assignment over the course of the treatment, although at times some accommodations have had to be made. In patients with preexisting chronic pain, whether back, neck, shoulder or other, this pain may worsen on treatment. Warning the patient of this possibility prior to treatment can help the patient prepare for the possible need for additional analgesics. We rarely use narcotics in this situation. During treatment, we are liberal with prescribing what our system calls "medical rec", where patients are allowed to get outside to walk but are not be expected to participate in the strenuous exercise such as basketball or other games.

Causes for fatigue developing during HCV treatment is often detected by laboratory evaluation. Conditions such as anemia, neutropenia, thrombocytopenia and thyroid abnormalities can be detected early with proper laboratory surveillance. Table 1 lists our routine laboratory monitoring schedule. The managing physicians review all laboratory tests.

Depression

Rates of depression during HCV treatment range from 16 to 36%.[1,2,6] At our largest facility, patients are reviewed by the psychiatrist or other mental health worker prior to treatment; at small facilities mental health screening is conducted by the primary care physician. No specific depression inventory is used. Exclusion from treatment on the basis of psychiatric reasons, specifically depression, is rare, but a patient with a history of depression with previous suicide attempts may be ruled out for therapy. It is also likely in our system that poorly-controlled psychotic patients do not get to the evaluation-for-treatment stage. The pre-treatment psychiatry visit does, however, alert the mental health team that HCV therapy is being considered so that some patients with pre-existing mental health problems maybe followed more closely during their HCV therapy. This pro-active approach has resulted in no patients stopping treatment for psychiatric side effects and there have been no suicide attempts in patients during treatment. There have been unusual personality changes in a small number of patients while on treatment; nonetheless these inmates were highly motivated to complete treatment and were successful in achieving SVR. During therapy anti-depressants, usually selective serotonin reuptake inhibitors (SSRIs), such as fluoxetin, are liberally prescribed. Although most psychotropic medicines in our facilities are prescribed by psychiatrists, patient management is conducted by primary care physicians. In our system, we do not use anti-depressants as prophylaxis for depression.

Nausea, anorexia, weight loss

The reported rates for nausea and/or anorexia range from 21 to 47%.[1,2,6] As part of our counseling, we inform patients that lighter weight people seem to do better with HCV treatment. Thus, the expected loss of appetite and weight may actually help achieve the desired long-term positive response. Usually the gastrointestinal symptoms associated with HCV treatment occur in the mornings, so by evening the patient is able to eat. If a normal weight patient begins losing weight we allow extra calories, usually as an evening snack, for weight stabilization. Patients with diabetes mellitus may need to reduce or stop hypoglycemic medication during HCV treatment, even if significant weight loss has not occurred. Costly nutritional supplement drinks are required only rarely.

Local skin reaction

A large number of our patients have a local skin reaction to the weekly pegylated interferon injections; the literature gives a range of 7 to 58% for this complication.[2,6] With this reaction, the injection site appears inflamed; edges of the reaction are not well demarcated. Effectiveness of steroid cream varies. As with other reactions, advising patients beforehand prepares them. The skin condition lasts throughout interferon therapy, but resolves over time upon completion.

Fever, chills, and rigor

Fever occurs in as many as 37 to 56% of patients and 23 to 43% experience chills/rigor.[1,2,6] Usually, these complaints can be managed with antipyretics. However, three of our patients had severe rigors associated with interferon injections. One male patient elected to quit therapy because rigors occurred with his first injection and he did not want to suffer it again. A female experiencing a similar severe rigor tried a second injection (timed away from her insulin injection to make sure a cross-reaction wasn't occurring), but after an almost shock-like reaction recurred, therapy was discontinued. A third patient had a similar reaction, but only after several months of treatment. He continued therapy and rigors did not occur with each injection.

Hematologic complications

Anemia, defined as a hemoglobin < 11.0 g/dL can occur in 19 to 36% of patients.[1,6] It is usually hemolytic in nature and related to the ribavirin. We use the nationally recommended parameters and schedule for ribavirin dose reduction for Hgb < 10.0 g/dL (Tables 2 and 3). Leukopenia, defined as WBC < 3.0 x 10^9/L, occurs in 17 to 45% of treated patients and is more commonly related to interferon.[1,6] Our current dose reduction parameters and schedule for WBC < 1.5 x 10^9/L or absolute neutrophil count < 0.75 x 10^9/L are noted in Tables 2 and 3. We have not needed to stop therapy in any of our patients due to anemia or leukopenia.

Thrombocytopenia, defined as platelets < 100 x 10^9/L occurs in 4 to 11% of patients.[1,6] Three of our patients had HCV therapy stopped for severe thrombocytopenia, with platelet counts < 50 x 10^9/L. Platelet transfusions are administered to patients with compensated cirrhosis who begin therapy with platelets < 100 x 10^9/L. Surprisingly many of these patients are able to continue treatment although the viral response rate is lower than others with healthier livers. To date, we have not used cellular growth factors, such as granulocyte colony stimulating factor (GCSF), to avoid lowering doses of either pegylated interferon or ribavirin, but we have recently revised our HCV treatment guidelines to add the use of erythropoietin to help prevent ribavirin dose reduction due to drug-induced anemia. The literature supports the importance of maintaining a full ribavirin dose early in treatment for best results. The importance of the full dose of pegylated interferon is not as clearly addressed in the literature, so we have not included the use of GCSF in our management. Although there are limited data suggesting GCSF can increase the number of WBCs in patients receiving HCV therapy and can thus permit higher interferon dosing, improvements in SVR have not yet been demonstrated.[7]

A major challenge to treating HCV in corrections is economic: can we afford these growth factors on top of the cost of HCV therapy itself? Our approach has been very conservative, but we added the erythropoeitin to our formulary with the reasoning that this will enhance success of an investment for treatment of $30,000 or more (for genotypes 1 and 4).

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Bacterial infections

One patient's HCV treatment was discontinued after three hospitalizations for cellulitis while on therapy. The infection first began in a tattoo acquired while on treatment. Our pre-treatment counseling specifically forbids the acquistion of new tattoos while on treatment, but on review of our consent form, it did not include this statement. Since this patient was insistent on continuing treatment and denied knowing of this mandate, treatment was initially continued; two additional episodes of infection ensued and treatment was terminated due to recurrent severe infections.

Severe jaundice

Although mild elevations of bilirubin are reported in 11 to 28% of patients,[6] severe elevations of bilirubin, defined as bilirubin > 12.0 mg/dL have not been reported. Therapy was discontinued in one or our patients experiencing severe jaundice with a bilirubin > 20 mg/dL while on treatment. His abdominal ultrasound was negative. He recovered well after stopping both medications and it was not clear which drug was the cause of this adverse event.

Decompensation of liver disease

One patient died after therapy had started. His pre-treatment liver biopsy showed stage 3 fibrosis and not cirrhosis, thus making him a candidate for treatment. Of note, his laboratory studies showed low platelets and a normal albumin. These were consistent with compensated cirrhosis, which did not show in his biopsy, likely due to sampling variability. His pre-treatment physical exam did show edema. A review of his care at a mortality conference after his death attributed his worsening liver disease to underdiagnosing cirrhosis, perhaps missed by biopsy. It is known that the biopsy only reaches small pieces of the liver and can underdiagnose severity of disease. Interestingly, he was a responder to treatment at both 12 and 24 weeks of care. Although his hemoglobin fell at the beginning of treatment, it was not below the threshold that triggers a change in the ribavirin dose. A later drop in hemoglobin, after six months of treatment did prompt a decrease in his ribavirin dose. Investigation for other etiologies accounting for the drop in hemoglobin such as gastrointestinal bleeding was not conducted. After eight weeks of treatment, his WBC decreased and required a reduction in the interferon dose. After 24 weeks the patient's WBC rose to 10.2 x 10^9/L but this was overlooked in terms of a search for an infectious source. After eight and a half months of treatment, he was hospitalized with an upper gastrointestinal bleed. HCV treatment was stopped, esophageal varices were diagnosed and portal hypertension was noted. He developed methicillin resistant S.aureus bacteremia secondary to an infected shoulder joint leading to acute renal failure and further hepatic failure. He continued to decompensate and expired of sepsis. This case illustrates not only the seriousness of liver dysfunction and the complexities of the management of such patients but also the limitations of HCV therapy in patients with more advanced liver disease.

Summary

It has been our experience that the vast majority of HCV-infected inmates receiving HCV therapy can complete their treatment without serious adverse events. Some of our success may be explained by our careful selection of patients to receive HCV therapy; however, our criteria for treatment are reasonable and inclusive. Further, few of our patients were HIV-HCV co-infected and rates of successful treatment completion in co-infected patients may differ from those we observed.

We have learned that managing the side effects of HCV therapy takes committed providers and an educated nursing team. It also requires pre-treatment education of the patient and reassurance about the unpleasant effects these strong medications can cause. Close and careful monitoring of laboratory parameters is necessary with orders for medication dose changes if needed. Awareness of the potential complications of HCV therapy and the management of these adverse effects is critical to maintaining therapy. Nonetheless, if these challenges are addressed, sustained virologic responses in patients on HCV treatment in corrections can match or exceed the responses of programs in our communities.

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Table 1. Laboratory Evaluations at Visit Week After Initiation of HCV Treatment (Genotype 1)

Lab Evalutation	During HCV Therapy													Post HCV Therapy			
	2	4	6	8	12	16	20	24	28	32	40	44	48	4	8	12	24
CBC/Diff/PLTS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
AST/ALT		X		X		X	X		X	X	X	X		X	X	X	X
Bilirubin Direct					X			X					X				X
PT/PTT					X			X					X				X
AFP					X			X					X				X
ANA					X			X					X				X
TSH					X			X					X				X
Uric acid					X			X					X				X
Triglycerides (fasting)					X			X					X				X
HCV (quantitative)					X			X					X				X

Table 2. Parameters for Dose Reduction

Parameter	Dose Reduction	Permanent Discontinuation of Treatment (Both pegylated interferon and ribavirin)
Hemoglobin	< 10 g/dL (Ribavirin)*	< 8.5 g/dL
White Blood Cell	< 1.5 x 10^9/L (Interferon)*	< 1.0 x 10^9/L
Neutrophil Count	< 0.75 x 10^9/L (Interferon)*	< 0.5 x 10^9/L
Platelet Count	< 80 x x 10^9/L (Interferon)*	< 50 x 10^9/L
Bilirubin Direct		> 2.5 x upper limit of normal
Bilibrubin Indirect	> 5 mg/dL (Ribavirin)*	> 4.5 mg/dL (for >4 weeks)
Creatinine		> 2.0 mg/dL
ALT / AST		> 2 x baseline AND > 19 x upper limit of normal

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Table 3. Dose Reduction

MEDICATION	INITIAL DOSE	TOTAL NO. OF CAPSULES/DOSES	REDUCED DOSE	TOTAL NO. OF CAPSULES/DOSES
Pegylated Interferon				
Pegasys	180 mcg SC/wk	NA	135 mcg SC/wk	NA
Peg-Intron	1.5 mcg/kg SC/wk		0.75mcg/kg SC/wk	
Ribavirin	800 mg QD	2 capsules am/	600 mg QD	1 capsule am/
		2 capsules pm	(dec. 200 at a time)	2 capsules pm
	1000mg QD(<75kg)	3 capsules am/	800mg QD	2 capsules am/
		2 capsules pm	(dec. 200 at a time)	2 capsules pm
	1200mg QD(>75kg)	3 capsules am	1000 mg QD	2 capsule am/
		3 capsules pm	(dec. 200 mg at a time)	3 capsules pm

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CASE STUDYS - HEPATITIS C THERAPY

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Case 1: Does this patient need HCV therapy?

A 45 year-old male inmate is diagnosed with HCV infection after he is found to have an elevated AST and ALT of 69 and 75 IU/L, respectively, on routine admission screening. His bilirubin is normal, and his albumin is 4.2 gm/dL. He feels well. He reports that he injected heroin for several years in his early twenties.

Question: How do we know whether or not this patient needs treatment for HCV?

Discussion

The first thing we should do is determine whether or not he has chronic HCV infection as 15-25% of people who are exposed and infected with HCV will clear the virus on their own. This is in contrast to hepatitis B virus (HBV) infection, where 90-95% of people will spontaneously clear hepatitis B DNA if infected as an adult. Chronic HCV infection is determined by ordering a viral load for HCV, known as an HCV RNA PCR. Given the patient's elevated transaminases and his history of injection drug use (IDU), his pre-test probability of having chronic HCV infection is high.
His viral load returns at 600,000 IU/mL, con-

firming chronic infection. If the viral load result is undetectable, the test should be repeated in 3-6 months for verification, and the patient would be confirmed as NOT having chronic infection, with no treatment necessary.

The next step in evaluation of a patient with HCV viremia - in addition to screening for other forms of hepatitis, including hepatitis A virus (HAV) infection, HBV infection, autoimmune liver disease, and HIV - would be an assessment of the genotype, or strain of HCV, and consideration of liver biopsy. It is important to remember that HCV-infected patients can have significant fibrosis and even cirrhosis, yet have normal transaminases (AST and ALT). The genotype helps determine the length of HCV therapy and the likelihood of treatment response. Patients with genotypes 2 or 3 are usually treated for 24 weeks, whereas patients with genotypes 1 or 4 are treated for 48 weeks. Most hepatitis specialists recommend a liver biopsy, though there are situations where a biopsy may not be needed, particularly if one plans to treat regardless of a biopsy result. Patients with genotypes 2 or 3 have such a favorable treatment response that the 2004 American Association for the Study of Liver Disease (AASLD) treatment guidelines state that a liver biopsy in such patients can be considered optional. A liver biopsy does carry bleeding risks and a small risk of death (1/10,000 deaths).

Treatment responses are poorer in patients with genotype 1. A liver biopsy can help determine how much scarring, or fibrosis, there is in the patient's liver and this information can be useful to the patient and clinician before and during HCV therapy. There are different scoring systems pathologists used for measuring liver fibrosis, and a com-

mon one is the Metavir fibrosis score (see HCV 101). The score ranges from F0 to F4, with F0 meaning no fibrosis and F4 signifying cirrhosis. If there is no fibrosis (Metavir F0), the patient does not need treatment and can be followed with a repeat biopsy in 3 to 5 years to look for progression. This is true regardless of the amount of inflammation seen in the biopsy (Metavir "A" score).

If on liver biopsy, the patient has a Metavir score of F1, some experts would recommend treatment and others would observe, with a repeat biopsy in three to five years. The 2002 National Institutes of Health (NIH) Consensus Panel on HCV recommended treatment for patients with Metavir scores of F1 or higher. Similar to the AASLD guidelines, if the patient's virus is genotypes 2 or 3, this panel felt that a liver biopsy would be optional and hence not critical to the evaluation. HCV genotypes 2 and 3 respond more favorablly than genotypes 1 and 4 and usually require a shorter course of treatment, unless HIV-co-infection is present. HIV-HCV co-infected patients have a higher relapse rate when treated for 24 weeks, so most experts recommend 48 weeks of treatment regardless of genotype for these patients.

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Liver biopsy results may also be helpful to patients during therapy. If adverse effects of HCV therapy emerge and threaten treatment discontinuation, patients with more severe pathology may feel motivated to preserve whereas those with relatively milder disease on biopsy can consider this when weighing the risks and benefits of continuing treatment.

If the patient has a coagulopathy, such as prolonged prothrombin time (PT) or thrombocytopenia, a biopsy can by done by an interventional radiologist via the transjugular approach. In cases where the patient declines a biopsy due to fear of the test or other concerns, treatment should not be withheld, regardless of genotype.

Some laboratories offer a panel of blood tests used as non-invasive markers of fibrosis, which might be helpful for patients who decline or can't receive a biopsy. These tests, however, are not as helpful as a biopsy. Some data also suggest that the ratio of the platelet count and serum albumin can be used to gauge liver fibrosis.

It is important to remember if the patient is not immune to HAV or HBV, vaccination for these should be offered so the patient does not acquire infection with another hepatitis-causing virus on top of the one he or she already has. Screening for treatment should also include assessing thyroid function, cardiac status, mental health, and overall medical history. A past history of depression or other mental illness should not necessarily preclude treatment; more important is an assessment of the patient's current mental health.

The history and physical exam can also give important information. Historical elements that are important include the length of time since a patient first injected drugs, and alcohol consumption. Most patients are infected with hepatitis C early on, often in their first year of injection drug use. Alcohol is a clear risk factor for progression of fibrosis, and patients should be advised to avoid all alcohol on release. The physical exam can reveals stigmata of cirrhosis, such as palmar erythema, spider angiomas, splenomegaly, and asterixis. Laboratory clues to cirrhosis include thrombocytopenia, low albumin, hyperbilirubinemia, and prolonged prothrombin time.

To summarize, if the patient has detectable viremia with HCV, obtain a genotype. If the genotype is 1 or 4, a biopsy is generally recommended, though not required, for treatment. If the patient has genotype 2 or 3, a biopsy is less critical as treatment duration is shorter and treatment responses are higher - advantages that favor treatment regardless of biopsy result. If on liver biopsy, the patient has more than portal fibrosis (Metavir F2 or higher) and does not have decompensated liver disease, treatment is indicated. The standard treatment is now pegylated interferon with ribavirin. Patients with genotype 1 or 4 are assessed after 12 weeks of combination therapy, and if they have a treatment response, designated as at least a 2-log10 decrease or an undetectable viral load, treatment should be continued for 36 more weeks, or 48 weeks total. For patients with genotypes 2 or 3, 24 weeks of combination therapy is recommended. A sustained virologic response (SVR) is determined when the patient's viral load remains undetectable 24 weeks after therapy is completed.

In this patient, a liver biopsy was performed and revealed a Metavir score of F2. He was found to be HIV-uninfected and susceptible to HAV. His HBV surface antibody and core antibody were both positive, indicating prior and resolved infection with that virus. His HCV genotype was 1 and he elected to start HCV therapy with ribavirin and interferon.

Case 2: HCV therapy in a patient with cirrhosis

A 48 year-old woman with chronic HCV infection undergoes a liver biopsy and is found to have cirrhosis with a Metavir score of F4. She has been incarcerated for two years, and started injecting drugs when she was 19 years old.

Question: Given that she has cirrhosis, can she be treated for her HCV?

Discussion

Cirrhosis can be broadly broken down into two categories, compensated and decompensated. Decompensated liver disease implies hepatic encephalopathy, uncontrolled ascites, bleeding varices, or any of the late-stage consequences of cirrhosis. Determination of the patient's Childs-Pugh Score is useful to determine whether a patient's cirrhosis is decompensated. (see HCV 101) Each element is scored and the points calculated, with the maximum being 15, the worst score. Child's class A is compensated (score 5 or 6), Child's Class B is early decompensated (score 7-9), and Child's Class C is decompensated (score of 10 or higher) cirrhosis. Decompensated cirrhosis can be worsened by treatment with interferon and ribavirin. Patients with compensated cirrhosis should only be treated with the input of a clinician experienced in the management of patients with HCV.

Patients with compensated cirrhosis may be treated with interferon and ribavirin, though they will require closer follow-up and more frequent laboratory monitoring to avoid untoward complications of therapy. Again, therapy should be undertaken only in conjunction with a clinician experienced in the management of such patients. Consideration for transplant listing should also be undertaken, if appropriate. Sustained virologic response rates are lower in patients with cirrhosis than in patients without cirrhosis. Patients with compensated cirrhosis typically have had stable liver disease for years and usually do not present often to sick-call or require hospitalization. As mentioned above, it is important to recognize that a subset of HCV-infected patients may have cirrhosis demonstrated by liver biopsy, yet have normal liver parameters, including normal transaminases and albumin. This is another reason many experts recommend a liver biopsy for patients with chronic HCV infection.

This patient has cirrhosis but no evidence of decompensated disease and. As such, she is a candidate for HCV therapy.

Case 3: Managing advanced liver disease

A 55 year-old male with chronic HCV infection returns to your facility after being hospitalized for fever, ascites and a 25-pound weight gain over the preceding two months. He is on spironolactone 50 mg po bid and

furosemide 40 mg po daily. He was treated for spontaneous bacterial peritonitis, and is now off antibiotics. He had an episode of confusion while hospitalized, and was found to have an ammonia level elevated at 50 Umol/L. He is now on lactulose 30 mL (20 gm) po bid. An upper endoscopy revealed moderate esophageal varices, and he was started on nadolol 20 mg po daily. He also has type 2 diabetes mellitus treated with an oral hypoglycemic, as well as chronic neuropathy pain, for which he had been on ibuprofen but for which he is now prescribed oxycodone.

Question: How should this patient be managed, and what signs/symptoms should you expect?

Discussion

This patient will most likely come to your infirmary initially. His fluid balance may not yet be fully stabilized, so he will need monitoring of his weight several times per week, as well as close follow-up of his electrolytes. Adjustments may still need to be made in his diuretic therapy. A low-salt diet is best, and the patient may have been discharged on fluid restrictions. This patient has decompensated liver disease, and hence, is not a candidate for interferon/ribavirin therapy.

In this type of patient, chronic acetaminophen therapy is contraindicated, as it may accumulate in his liver and cause additional problems. Furthermore, many such patients typically have thrombocytopenia and prolonged prothrombin times, increasing their bleeding risk. For patients with esophageal or gastric varices, aspirin and non-steroidal anti-inflammatory medications are also relatively contraindicated, so as to avoid bleeding complications. In addition, concomitant gastritis or duodenitis is common, and patients may require an H2-blocker or proton-pump inhibitor therapy. Oxycodone or low-dose morphine preparations, either short- or long-acting, may be appropriate analgesics to control chronic pain. Finally, these patients are at risk for renal failure (hepatorenal syndrome) and as they are often on diuretic therapy non-steroidal medications pose further risk.

Hepatic encephalopathy is often managed with lactulose. The goal is to titrate the lactulose to soft/loose stools without severe diarrhea to help eliminate hepatic by-products. The level of serum ammonia elevation

HEPATITIS C VIRUS (HCV) THERAPY
(continued from page 6)

does not correlate well with the degree of encephalopathy. Once a patient has been diagnosed with hepatic encephalopathy, clinical monitoring will be more useful than following ammonia levels. Medications that depress central nervous system function, such as benzodiazepines, should be avoided as much as possible. Other medications that may be prescribed in patients to reduce the effects of hepatic encephalopathy include antibiotics such as neomycin, metronidazole, or rifaximin - a nonabsorbable derivative of rifampin.

Patients with varices will often be prescribed a beta-blocker, as in this case, in an attempt to decrease portal pressure and reduce bleeding risks. Some clinicians may also recommend antibiotic prophylaxis for patients with ascites to prevent spontaneous bacterial peritonitis, particularly if the patient has had a previous episode of peritonitis. Antibiotic prophylaxis has not been shown to confer a survival advantage, however.

This type of patient should be considered for orthotopic transplantation evaluation, if available. His clinicians must discuss with the patient the severity and life-threatening nature of his illness, as well as health care proxy and resuscitation wishes. Life expectancy will be greatly reduced and may be measured in months to years.

References

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HCV101

Child-Pugh Classification

Modified Child-Pugh classification of severity of liver disease according to the degree of bilirubin, albumin, the prothrombin time, ascites, and encephalopathy.

Measure	1 point	2 points	3 points
Bilirubin mg/dL	<2	2.0 - 3.0	>3
Albumin g/dL	>3.5	2.8-3.5	<2.8
Prothrombin Time			
Seconds Over Control	1.0-3.0	4.0-6.0	>6
INR	<1.8	1.8-2.3	>2.3
Ascites	None	Slight	Moderate
Hepatic encephalopathy	None	Grade 1-2	Grade 3-4

Grade	Points	1 yr patient survival %	2 yr patient survival %
A: well-compensated disease	5.0-6.0	100	85
B: significant functional compromise	7.0-9.0	80	60
C: descompensated disease	10.0-15.0	45	35

Metavir Scoring System

Stage	Amount of Scarring
0	No Scarring
1	Minimal Scarring
2	Scarring has occurred and extends beyond the areas of the liver that contain blood vessels
3	Bridging Fibrosis is spreading and conecting to other areas that contain fibrosis
4	Cirrhosis or advanced scarring of the liver

RESOURCES

Slides from the NCCHC Pre-conference Seminar
Infectious Diseases in Corrections: An Expert Panel
October 28, 2006
http://www.idcronline.org/archives.html

Bureau of Justice Prison Statistics Hepatitis Testing and Treatment
http://www.ojp.usdoj.gov/bjs/abstract/httsp.htm

Federal Bureau of Prisons Viral Hepatitis Clinical Practice Guidelines
http://www.bop.gov/news/medresources.jsp

National HCV Prison Coalition
http://www.hcvinprison.org/

Department of Health and Human Services
2006 Adult and Adolescent Antiretroviral Treatment Guidelines
http://www.aidsinfo.nih.gov/guidelines/

International AIDS Society-USA Panel
2006 Recommendations of the Treatment for Adult HIV Infection
http://jama.ama-assn.org/cgi/content/full/296/7/827

CDC's Revised Recommendations for HIV Testing of Adults, Adolescents, and Pregnant Women in Health-Care Settings
http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5514a1.htm

American Academy of HIV Medicine
http://www.aahivm.org/

NEWS AND LITERATURE REVIEWS

Factors Associated with Seronegative Chronic Hepatitis C Virus (HCV) Infection in HIV Infection

HIV-infected individuals may not mount typical serologic responses to infections including HCV. This group of investigators sets out to determine the prevalence of chronic seronegative HCV infection in a large, multi-center, nationally representative cohort of HIV-infected men and women (The FRAM Cohort). Their results, published in *Clinical Infectious Diseases*, demonstrate that among the 1,174 anti-HCV-negative study particpants, the prevalence of seronegative HCV infection as determined by HCV RNA testing was 3.2%. Notably, by multivariate logistic regression analysis, the researchers were able to determine factors associated with HCV RNA positivity in anti-HCV-negative subjects. These factors were history of injection drug use (IDU), higher alanine aminotransferase (ALT) levels, and CD4+ cell counts <200 cells/l. Among those HIV-infected individuals with a history of IDU and either an abnormal ALT level or CD4+ cell count <200 cells/l, the prevalence of seronegative HCV infection was 24%. The authors suggest that the low overall prevalence of seronegative HCV infection, while still greater than reported prevalence in HIV-uninfected patients, demonstrates that the HCV EIA 2.0 assay, commonly used in many institutions, is a sufficiently sensitive screening tool to determine antibody status. However, the findings suggest that HCV RNA testing should be performed in anti-HCV-negative HIV-infected patients, especially those with a history of IDU and either a CD4+ cell count <200 cells/l or an abnormal ALT level.

Factors Associated with Seronegative Chronic Hepatitis C Virus Infection in HIV Infection. Chamie, G et al. Clinical Infectious Diseases 2007;44:577-583.

Estimating the Future Health Burden of Chronic Hepatitis C and Human Immunodeficiency Virus Infection in the United States

Using two back calculation models, Deuffic-Burban et al. estimated the future disease burden of HCV and HIV infections in the United States. The study, the first of its kind to account for antiviral treatment advances, utilized United States epidemiological data from the Centers for Disease Control and Prevention (CDC) and the World Health Organization (WHO). Based on past incidence, it appears that the HCV incidence in the peaked in 1984 at 350,000 new infections then fell to 77,000 in 1998, while HIV incidence reached a maximum in 1989 at 142,000 new infections before declining to 79,000 in 1998. Looking forward, the investigators estimate that mortality related to HCV, defined as death from liver failure or hepatocellular carcinoma, will peak at nearly 13,000 in the 2030, having risen from only 3,700 in 1998. The authors assert that predicted HCV mortality will fall only if there is increased access to treatment or more effective antiviral development. In comparison, HIV-related mortality will drop to approximately 4,200 in 2030, down from 14,400 in 1998. These results showcase the decline in HIV-related mortality due to the effectiveness of HAART, but highlight the growing burden HCV-related death over the next twenty-five years.

Estimating the Future Health Burden of Chronic Hepatitis C and Human Immunodeficiency Virus Infection in the United States. Deuffic-Burban et al. Journal of Viral Hepatitis 2007;14:107-115.

Do Condoms Cause Rape and Mayhem? The Long-Term Effects of Condoms in New South Wales' Prisons

Researchers from Australia, seeking to address the concerns of politicians, prison staff, and inmates, examined the long-term effects of the introduction of condoms and dental dams into New South Wales' prisons. Their findings, published in *Sexually Transmitted Infections*, demonstrate that most of the concerns regarding condoms in prisons were not realized. In contrast to the general expectations, the investigators reported an overall decrease in both self-reported consensual male-to-male sex as well as male sexual assaults over the five year period condoms became available to inmates. While there were reported incidents of prisoners using condoms to conceal contraband material, such as tobacco, there was no associated increase in IDU. Additionally, the fear that condoms would be used as weapons was not born out, as there were only three reported incidents of condoms being used in assaults; none of which were serious. The data were derived from Inmate Health Surveys of randomly selected prisoners from all prisons and official New South Wales Department of Corrective Services' reports taken at the beginning of the distribution program in 1996 and then again in 2001. The authors note that the decrease in both consensual sex and sexual assault among male prisoners may be due to other factors, including the introduction of an HIV/AIDS education program in 1996. However, they suggest that the presence of condoms in the prisons may have further raised awareness and reinforced the prevention messages. The investigators conclude that the introduction of condoms did not cause the mayhem that many had feared and note that opposition to the distribution program soon dissipated.

Do Condoms Cause Rape and Mayhem? The Long-Term Effects of Condoms in New South Wales' Prisons. Yap, L et al. Sexually Transmitted Infections published online 19 Dec 2006.

Reduction in Triglyceride Level With N-3 Polyunsaturated Fatty Acids in HIV-Infected Patients Taking Potent Antiretroviral Therapy

Hypertriglyceridemia is the hallmark dyslipidemia associated with HIV infection. N-3 polyunsaturated fatty acids (PUFAs), such as fish oil, have been found to reduce triglyceride levels in HIV un-infected patients. This double blind, randomized study assessed the evolution of triglyceride levels in HIV-infected patients receiving stable HAART treated with fish oil. One hundred and twenty-two patients with baseline triglyceride levels between 200-1000 mg/dL were randomized for eight weeks to fish oil (2 g of fish oil three times daily) or placebo. At week eight, the median change in triglyceride levels was -25.5% in the fish oil group versus 1% in the placebo group. Triglyceride levels were normalized in 22.4% of the fish oil group, as opposed to only 6.5% of the placebo group. An eight week open label phase, during which all patients received fish oil supplementation, followed the initial eight week randomized period. The decrease in triglyceride levels was sustained in the original group assigned fish oil at week 16, whereas a 21.2% decrease occurred for patients in the placebo group who were switched to active drug at week 8. Significantly, the incidence of adverse events during the randomized double blind study period was not more frequent in the fish oil group; minor gastrointestinal disorders without vomiting being most common. Additionally, CD4+, CD8+ and viral load measurements were stable throughout the study. The authors suggest these results, which are comparable to previous randomized, open-label studies, demonstrate the efficacy and safety of fish oil to reduce some of the risk associated with hypertriglyceridemia in HIV-infected patients on HAART.

Reduction in Triglyceride Level With N-3 Polyunsaturated Fatty Acids in HIV-Infected Patients Taking Potent Antiretroviral Therapy. Truchis, P et al. J AIDS. 2007.

Complied by Ross Boyce

SELF-ASSESSMENT TEST FOR CONTINUING MEDICAL EDUCATION CREDIT

This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for continuing Medical Education through the joint sponsorship of Medical Education Collaborative, Inc. (MEC) and *IDCR*. MEC is accredited by the ACCME to provide continuing medical education for physicians.

Medical Education Collaborative designates this educational activity for a maximum of 1 AMA PRA Category 1 Credit(s)™. Physicians should only claim credit commensurate with the extent of their participation in the activity. Statements of credit will be mailed within 6 to 8 weeks following the program.

Objectives:
- The learner will be able to describe the common side effects of hepatitis-C therapy.
- The learner will be able to identify the parameters for discontinuation of hepatitis-C therapy.
- The learner will be able to identify commonly prescribed medications for various side effects of hepatitis-C therapy.

1. Which of the following is NOT a common side-effect of hepatitis C therapy:
   - A. Fatigue
   - B. Chronic diarrhea
   - C. Headache
   - D. Malaise
   - E. Arthralgias

2. Which of the following parameters requires the permanent discontinuation of treatment for patients receiving hepatitis C therapy:
   - A. White blood cell count of < 1.0 x 109/L
   - B. Bilirubin Direct of >2.5 x upper limit of normal
   - C. Hemoglobin of <8.5 g/dL
   - D. ALT >1.5 mg/dL

3. Detection of decompensated cirrhosis in a patient with HCV infection is an indication for ribavirin and interferon.

   TRUE or FALSE?

4. Lactulose, neomycin, metronidazole, and rifaximin, are all medication's that can be used for which of the following:
   - A. Hepatic encephalopathy
   - B. Thrombocytopenia
   - C. esophageal varices
   - D. All the above

5. According the results reported by Chamie, G et al., seronegative HCV infection in patients with HIV is more likely in all the following situations EXCEPT:
   - A. CD4+ cell count less than 200/uL
   - B. History of injection drug use
   - C. Hepatitis B virus co-infection
   - D. None of the above

In order to receive credit, participants must score at least a 70% on the post test and submit it along with the credit application and evaluation form to the address/fax number indicated. Statements of credit will be mailed within 6-8 weeks following the program.

Instructions:
- Applications for Credit will be accepted until February 28, 2008.
- Late applications will not be accepted.
- Please anticipate 6-8 weeks to recieve your certificate.

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COURSE EVALUATION

I. Please evaluate this educational activity by checking the appropriate box:

Activity Evaluation					
	Excellent	*Very Good*	*Good*	*Fair*	*Poor*
Faculty					
Content					
How well did this activity avoid commercial bias and present content that was fair and balanced?					
What is the likelihood you will change the way you practice based on what you learned in this activity?					
Overall, how would you rate this activity?					

II. Course Objectives

Were the following overall course objectives met? At the conclusion of this presentation, are you able to:

- The learner will be able to describe the common side effects of hepatitis-C therapy.　　**YES　　NO　　SOMEWHAT**
- The learner will be able to identify the parameters for discontinuation of hepatitis-C therapy.　　**YES　　NO　　SOMEWHAT**
- The learner will be able to identify commonly prescribed medications for various side effects　　**YES　　NO　　SOMEWHAT**
   of hepatitis-C therapy.

III. Additional Questions

a. Suggested topics and/or speakers you would like for future activities.

_____

b. Additional Comments

_____

_____