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INFECTIOUS DISEASE ALERT®

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Hope for Hepatitis C

ABSTRACTS & COMMENTARY

Sources: McHutchison JG, et al. Interferon alfa-2b alone or in combination with ribavirin as initial treatment for chronic Hepatitis C. *N Engl J Med* 1998;339(21):1485-1492; Davis GL, et al. Interferon alpha-2b alone or in combination with ribavirin for the treatment of relapse of chronic hepatitis C. *N Engl J Med* 1998;339(21):1493-1499.

A consortium of hepatology centers put together several large series of patients treated with interferon with or without ribavirin. The first report was of 912 previously interferon-naïve patients treated with interferon three times weekly plus placebo, or interferon three times weekly, plus 1000-1200 mg of oral ribavirin daily for 24 or 48 weeks. The population studied was the usual for hepatitis C in the United States with an average age in the mid 40s, twice as many males as females, and an average infection period of 19 years. Half of the patients acknowledged drug use as the source of infection, while one-third indicated an unknown source. One-third of patients already had bridging fibrosis on liver biopsies done at the start of therapy. More than 1300 patients had to be screened to find the 900 patients due to exclusion factors such as HIV infection, seizures, serious emotional disorders, azotemia, and ongoing drug or alcohol abuse.

The dropout rate was 9% for the 24-week treatment program and 16% for 48 weeks. Among the symptoms listed for those who dropped out were anxiety (15%), depression (30%), insomnia (30%), and alopecia (30%). Ribavirin was not associated with an increase in depression or psychiatric symptoms but was associated with anemia with a fall in hemoglobin to 10 g/dL or less in 8% of patients. There was also some associated leukopenia and thrombocytopenia.

Of those treated with interferon alone, the virus was shown to be eliminated by PCR in only 6% of those who received 24 weeks of therapy and in 13% of those who received 48 weeks. The addition of ribavirin (compared to placebo) increased the response rates to 31% and 38% for the same intervals. There also seemed to be a comparable response in follow-up liver biopsy results with ribavirin and longer duration of therapy. Poor response was correlated with

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genotype 1, high initial viral load, and cirrhosis at onset.

The second article examined 354 patients who had relapsed after having had a normal serum alanine aminotransferase after one or two prior courses of interferon therapy. They were randomized to receive interferon three times weekly plus either ribavirin or placebo for 24 weeks. The elimination rate of virus by PCR after an additional 24 weeks was 5% for those who received interferon alone and 49% for those who received interferon with ribavirin. This group also tolerated the medication relatively well.

COMMENT BY ALAN D. TICE, MD, FACP

These studies provide some reason for greater optimism for the treatment of hepatitis C, which is thought to infect about 4 million Americans and 100 million people around the world. Prior results of therapy with interferon alone have been disappointing although it has been FDA approved.

The recent national hepatitis C campaigns by the CDC and others have clearly heightened awareness and will continue to do so—especially with the involvement of the blood banks with their "look back" programs. The recent CDC guidelines for the screening of patients for hepatitis C are useful although still somewhat controversial.[1]

While the addition of ribavirin looks relatively good compared to the standard regimen of interferon alone, it is important to recognize the cost of therapy as well as the side effects. It is clearly a problem trying to treat everyone with hepatitis C when some have liver failure, continue to drink alcohol, or have serious underlying diseases—especially at a cost of about $10,000 per year for interferon alone. The effect on the prison system alone in the United States would be overwhelming if all of the estimated 400,000 inmates with hepatitis C were treated. Not every patient is, however, a good candidate for therapy. With the studies reviewed here, one-third of the patients who were screened were excluded from therapy—usually for good reasons.

On the other hand, there are patients who clearly would benefit from treatment but may not even realize they are infected.

The implications of these studies in regard to the duration of therapy are interesting. It has been hoped that a determination of those who are not going to respond would become apparent by measuring viral load a month or possibly more after therapy is initiated. This did not seem to be possible in the first study as those who were treated for 48 weeks were more likely to respond than if they were treated for 24 weeks with ribavirin or not.

There is also a need to examine the optimal use of interferon with ribavirin. Longer courses of therapy seem to be beneficial. Daily dosing may be more effective and better tolerated. Reducing iron load may be helpful. It may be worth treating relapsers and nonresponders again. It is interesting that relapsers had a higher rate of response than those who had not previously received interferon. Further studies on interferon use are ongoing and should be helpful.

In the long term, the search is underway for newer and better agents to treat hepatitis C. There are trials ongoing with a pegylated interferon that can be given once a week. Helicase inhibitors and other new antiviral agents are being studied with the investigations of new drugs spurred on by HIV. Unfortunately, there seems to be no value to the other presently available anti-retrovirals for hepatitis C (as opposed to hepatitis B). In fact, they may be detrimental for people coinfected with hepatitis C and HIV. In terms of alternative medicine therapy for hepatitis C, there has been a nice study of over-the-counter thymic extract reported in the *Annals of Internal Medicine*, which shows it has no value compared to placebo—despite claims in the media and on the Internet.[2] ❖

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2. Raymond RS, Fallon MB, Abrams GA. *Ann Intern Med* 1998;129(10):797-800.

Which of the following is the most common side effect of ribavirin administration to patients with hepatitis C infection?

a. Anemia
b. Leukopenia
c. Thrombocytopenia
d. Depression

More Bad News: Even Orange Juice is a Risk for *Salmonellosis*!

ABSTRACT & COMMENTARY

Synopsis: *An outbreak of Salmonella serotype hartford infections associated with unpasturized orange juice is reported.*

Source: Cook KA, et al. Outbreak of Salmonella serotype Hartford infections associated with unpasteurized orange juice. *JAMA* 1998;280:1504-1509.

A review of the *Salmonella* serotype-based surveillance system by the New Jersey Department of Health in June 1995 identified a cluster of *Salmonella hartford* infections among seven unrelated New Jersey residents returning from a theme park in Orlando during May 1995. This initiated an investigation into the source and extent of the outbreak.

Cases were found in the CDC's national *Salmonella* surveillance system from reports of *Salmonella hartford* since May 1995. Cases were designated as a confirmed (*S. hartford* infection) or probable (*Salmonella* serogroup C1) infection in residents of visitors to Orlando in May or June 1995.

A matched case-control study was conducted to identify risk factors. All cases were limited to visitors to the theme park's hotel because most of the patients had stayed at one of the 13 hotels. There were about three controls per case (with no history of diarrhea or vomiting during or within 7 days of the visit) who were matched for age, group, hotel, check-in date, and number of days spent visiting the theme park.

A total of 62 patients from 21 states were identified. Of the 32 patients enrolled in the study, 31 (97%) ill persons drank orange juice compared with 43 (54%) of 80 matched controls (matched odds ratio, undefined; 95% confidence interval, 5.2 to undefined; $P < 0.001$). Even though eating waffles was also statistically significant by univariate analysis, a significant positive association between orange juice and illness remained after those persons eating waffles (16/30, 53%) were excluded from analysis.

The only specific event or meal associated with illness was "character breakfasts" served in the theme park, which had been attended by 29 of 32 (91%) of ill persons compared with 48 (58%) of 83 controls. No other activities or attractions in the Orlando area such as swimming in water parks and hotel pools or direct contact with animals were associated with illness.

Of all orange juice served at the theme park and all orange juice served at the character breakfast, 88% was purchased from a local juice processor and was unpasteurized. Site inspection of the processing plant that provided all of the orange juice to the theme park identified several deficiencies. The processing room was poorly sealed from the environment and rodent and bird droppings were present and there were reports of frogs being observed around the equipment. Several serotypes of *Salmonella* were isolated from in and around the plant and orange groves providing the majority of oranges, including *S. hartford* from a toad found just outside the juice processing plant.

The pH of orange juice samples ranged from 4.1-4.5 (mean 4.3), less acidic than the average pH of Florida oranges (3.7) but within the FDA accepted pH level (4.6). All juice samples contained coliforms and *Salmonella gaminara* was cultured from 10 (83%) of 12 juice containers representing four lots produced in May and July 1995.

All isolates tested (human, orange juice, and toad) were susceptible to all antimicrobials tested. Seven representative human isolates were indistinguishable by PFGE; however, the PFGE patterns of the orange juice, toad isolates, and nine reference isolates were different from the outbreak strain.

COMMENT BY JOSEPH F. JOHN, MD & PHILIP MATHEW, MD

Woe be to those of us who love freshly squeezed orange juice! Now we need to make sure it is pasteurized since, as shown by this crafty, case-controlled study, there are suppliers who do not pasteurize their products. Furthermore, there is apparently significant contamination with *Salmonella* in the animal environment of Florida orange groves, particularly with amphibian excreta. Although the tree frog feces contained strains of *Salmonella* whose PFGE did not perfectly match the PFGE type of the outbreak strain, there were a limited number of frog strains studied. Perhaps we will be treated to a follow-up paper on the variety of *Salmonella* strains in Florida orange grove frogs, looking carefully of course for *S. hartford* serotype. And when the frog study is complete, we will also have the pleasure of knowing the path-

ogenic flora of insects, birds, and mammals.

The contamination probably came from the ground of the grove whence the orange lited, or from the processing plant. The orange peel and rind are removed mechanically before the squeezing occurred, but residue from potentially contaminated peel and rind remained on the equipment. Production capacity is huge—40,000 liters per day. So, even though pasteurization at the final stage of juice production should remove the *Salmonellae*, there is a large volume of product that will require quality control. It would be interesting to know the potential daily volumes from the first orange-associated outbreak of *salmonellosis*, this one causing typhoid at a hotel in Cleveland in 1944 (*Am J Pub Health* 1946;36:34-36).

Orange juice incriminated in this outbreak came from at least four growers not related by common water sources or picking crews. The groves were up to 60 miles apart. The product was distributed beyond the theme park but just how broadly distributed we do not know.

On our most recently purchased gallon of orange juice (back here in New Jersey), I noticed the inscription clearly printed on the pull off tab: PASTEURIZED. *(Dr. Mathew is Senior Fellow, Robert Wood Johnson Medical School, New Brunswick, NJ.)* ❖

What is the most likely process that would ensure *Salmonella*-free orange juice reaching the consumer?

a. Hire more hygenic orange picking crews
b. Remove all amphibians from the orange grove
c. Package the freshly squeezed juice more quickly at the plant
d. Implement pasteurization of the final product

Summaries from the American Association for the Study of Liver Diseases Conference

CONFERENCE COVERAGE

Synopsis: *The American Association for the Study of Liver Diseases (AASLD) met in Chicago, IL, on Nov. 4-6, 1998. Abstracts are published in Hepatology (1998;28[4]:Supplement 1). Historically, this is the preeminent meeting for presentation of data on the epidemiology, pathogenesis, treatment, and resistance issues relating to all hepatitis viruses. The predominant forces in the field remain the pathologists and hepatologists, although infectious disease specialists are beginning to make a small mark. It is no surprise to learn that as treatments improve, the key clinical management issues relate to the realm of infectious diseases: viral load, resistance, etc. A total of 2440 abstracts were published and 1721 accepted for presentation, so the summary that follows touches only on selected teaching points. —Stephen L. Sacks, MD, FRCP*

Several key features of basic management paradigms of hepatitis B and C shifted significantly, or at least began to shift, during this important meeting. Hepatitis C is a common and important disease, soon to manifest itself in large numbers emanating from transient injection drug use (IDU) during the 60s and 70s. Sexual transmission of HCV was also confirmed here as a common source of transmission. In fact, it ranks only second in frequency to IDU. Other routes not always included in the list include cocaine snorting, endoscopy, and medical use of needles in countries not adherent to strict rules of sterilization (e.g., patients treated for schistosomiasis are at extremely high risk).

Dozens of studies examined the combination of interferon alpha and ribavirin for the management of hepatitis C. In fact, there is no question that this combination significantly increases the proportion of patients responding to treatment compared with interferon alpha alone. The combination also increases the proportion who escape relapse when therapy is withdrawn. Viral loads seem to decrease within several hours of the first interferon injection and then rebound a bit during the skipped day before the next injection, then, in a biphasic curve, head quickly to undetectable in responding patients. Prolonged half-life interferons, such as pegylated interferons, may obviate the need for continuous interruption of the antiviral effects that may, in turn, increase response rates.

Previous data have shown that HCV PCR RNA should be negative within 12 weeks after commencement of interferon alone. Patients not fully responsive (to interferon alone) by this point are very unlikely to respond—ever. Interestingly, the decision to pull therapy should probably be delayed in patients on combination therapy until five or six months. This is not because ribavirin slows the antiviral response, but rather because it pushes more patients with high viral loads into the category of potential responders and they may take longer to reach baseline—often doing so during the second three months of therapy. Patients on combination who have not responded by six months are unlikely to benefit from continuing treatment. A number of hepatology magic rules then intervene that are less well grounded on data. Many would consider an ALT response to the normal range as favorable, even in the absence of an antiviral response. These individuals will often retain ALT normality for some time after treatment withdrawal, even in the face of renewed viral replication. Other studies suggest that ALT should not be used

to make treatment withdrawal decisions.

Combination therapy is more effective than simple alpha interferon therapy in relapsers (respond to interferon but relapse on withdrawal) but is also more effective (in decreasing orders of magnitude of efficacy) in treatment-naïve patients and even to some extent, in nonresponders. Should a nonresponsive patient be encouraged to face another year of interferon side effects and treatment costs for a low but measurable increase in the chances of recovery? This is not settled. Treatment still needs to be individualized. Ironically, the best responders are those with the least aggressive liver disease.

An exciting set of findings, however, demonstrated the relative consensus of data suggesting that type II and type III genotypes of HCV respond more quickly and more often. It appears appropriate to discontinue combination therapy in patients with these genotypes at six months without altering response rates, thereby saving a full six months' of drug expense and toxicity. It is clear, then, that a pretreatment genotype will save a significant amount of money and morbidity in non-type-I patients. Patients with genotype 1 HCV can be pulled from treatment at six months if they are failing combination therapy, as defined by at least a continuing positive PCR RNA, since they will continue to fail. If ALTs have normalized and viral load is still measurable, you may have a hard time stopping therapy, but there is a paucity of data to support continuation. Patients with genotype I HCV who have a complete loss of viral load at 5-6 months should be continued on combination therapy for a full 48 weeks. Since type 1 (a and b) is the most common in the United States, it is important to discriminate genotype in understandng the plethora of published and presented data in this field.

Many current studies will still use interferon alpha, alone, in various doses. Expectations and predictors for treatment response are different for those using interferon alone compared with combination therapy. Ribavirin is generally well-tolerated, but causes a significant anemia in many, requiring drug withdrawal or dose reductions in some cases. If insurance is able to pay and the situation calls for this, erythropoetin is worth trying in patients who need treatment but cannot tolerate their hemoglobin drop. The cost of erythropoetin, however, is often prohibitive. The highest risk patients for fibrosis and progression to cirrhosis and hepatocellular carcinoma (which requires cirrhosis in HCV) are males, older than 40, with existing severe liver disease. One study suggests that the gamma GT to ALT ratio is inversely proportional to the treatment response rate. African Americans clearly do not respond well to interferon and respond poorly to combination therapy. Accordingly, it may not be justified to use the current drug regimens in most African American patients. Japanese data suggest that interferon somehow prevents some hepatocellular HCC even when it fails to resolve hepatitis.

New interferons are on the horizon, including pegylated interferons (given less often with prolonged half-lives) and consensus interferons engineered to mimic all the human interferon subtypes. Early data suggest that both are more effective than interferon alpha alone. Accordingly, combinations of one of these new interferons with ribavirin offer hope of even better response rates, perhaps driving expectations in naïve patients more than 50% in the near term. In counseling your patients, know that most (80-90%) patients with undetectable RNA by PCR six months after treatment withdrawal will sustain that response over the long-term. The much studied amantadine has no mechanistic rationale for effectiveness in HCV. Clinical studies confirm the absence of activity as a single agent or as a mixture with interferon alpha. Furthermore, prednisone withdrawal works just as poorly in HCV as has been shown previously with HBV.

Clinical management of patients with HCV requires knowledge of many psychosocial factors. Fatigue is a common symptom and has been thought to result from changes in central neurotransmission (*Hepatology* 1997; 25:492-494). Jones and Yurdaydin were not able to show a correlation between fatigue in HCV and decreased physical activity. Depression is a common cofactor in HCV. One study demonstrated psychological disorders in two of three HCV patients. Severity of fatigue, however, is independent of the presence of depression or anxiety, or surprisingly, the severity of underlying liver disease. The degree of dysfunction induced by fatigue, however, correlates well with underlying depression. Depression is often worsened by interferon and suicide is also a potential risk. Nevertheless, Jones and Yurdaydin treated HCV patients with serious psychiatric disease and found that treatment increased morbidity only modestly and, with close psychiatric observation, was manageable. Another study of fatigue showed correlations with age older than 40, female gender, heavy drinkers, and those with extensive liver fibrosis. Fatigue was associated with arthralgia, myalgia, paresthesia, and pruritis, but not with cryoglobulinemia, genotype, or histological activity scores.

What about long-term prognosis? Looking at all-comers, Seeff and colleagues (Seeff LB, et al. *N Engl J Med* 1992;327:1906-1911) followed up on their classical study showing no change in mortality overall by following patients for an additional five years. Again, there was no difference in overall mortality, although there appeared to be a difference in liver-related mortality identified in the follow-up. In understanding the Seeff data, it is important to note that the so-called benign out-

come of patients with HCV in these studies refers to all persons infected, including those who spontaneously clear the virus and those who never develop abnormal liver function tests. These are not the patients presenting to our offices for treatment who are already selected to some extent. Unfortunately, we still have no reliable prognostic indicators to predict outcomes for the patients who present for treatment with elevated ALTs and positive HCV PVR RNA. In a study from Argentina, the majority of patients (post-transfusion-related HCV) developed a slowly progressive disease with cirrhosis in more than 30%. All HCC followed cirrhosis in this study. There is no question that only a small proportion of the overall population of infected persons with HCV will not have a benign outcome. Unfortunately, the predictive factors are general and statistical and cannot be translated to the individual case where clearly, some risk of serious sequelae exists.

Hepatitis B is more treatable now. The good news: most patients respond to lamivudine at 100 mg daily. This drug is well tolerated and effective. A small proportion of patients will develop antiHBe and lose HBeAg with treatment and in about half of those, seroconversion will persist. Rarely, a patient will seroconvert also to anti-HBs. It appears that worrisome elevated ALTs on treatment or at treatment withdrawal are just as common in placebo recipients. However, some ALT rise is expected 12 weeks after treatment is stopped. Treatment reduces the DNA and ALTs of HBeAg-negative patients also (precore mutants and others). To qualify for treatment, patients should have a measurable HBV DNA by a non-PCR test. These are relatively insensitive and a positive result apparently reflects a significant viral load worthy of treatment. To my knowledge, it is not yet clear that those with lower viral loads should not also receive treatment but this has not been adequately studied. It is clear that responders to lamivudine do well, benefiting from reduced ALTs and improved histologies. However, be wary of data showing glowing histology rates, since most patients who fail to respond to treatments drop out and move on, leaving the success stories to be rebiopsied happily at the conclusion of studies. We see few histologies on the true failures. This has been the model for both HBV and HCV treatment protocols.

The bad news is resistance. A Chinese patient population treated over a two-year period saw a 61% incidence of resistance to lamivudine. Others have found the one-year rate to be 15% and the two-year rate to be about 30%. HBV develops resistance to lamivudine in the same place as HIV, the YMDD sequence of the reverse transcriptase. Such strains may be less virulent in vitro and patients with breakthroughs of resistance often (but not always) maintain lower HBV DNAs and ALTs quantitatively than they did prior to therapy. Does this justify maintenance of therapy in the face of resistance? This is not proven and is reminiscent of the black magic of HCV treatment. Don't forget, it took years to demonstrate that HIV resistance was clinically meaningful. Lamivudine and lamivudine plus HBIG have been effective in reducing the incidence of fibrosing cholestatic hepatitis (FCH) following transplantation for HBV. However, resistance rates are even higher here and with HIV, as one would expect. Resistance often results in liver failure or FCH in this setting.

New drugs are desperately needed. Until AASLD, hope was held for famciclovir 500 mg tid as an alternative or as a synergistic agent in combination. Once again demonstrating the importance of the properly controlled, randomized trial, several abstracts at this meeting showed that famciclovir is an inferior drug to lamivudine in clinical trials. DNA levels are reduced but only partially overall. A large proportion of patients do not ever respond and among those who do, resistance is also possible. In any event, famciclovir has not been shown to reverse clinical disease and probably has no future in the management of HBV.

But, there are important new drugs. Adefovir dipivoxil (Gilead Sciences) and lobucavir (Bristol-Myers Squibb) are in clinical trials. Phase II studies of either were positive with good reductions of viral load (approximately 3-4 logs) good clinical responsiveness, minimal side effects, etc. Phase III's are now in progress. Preclinical studies of BMS 200, 475—a new agent—support an incredible potency with more than a 7 log drop in animals. Lamivudine-resistant strains are susceptible in vitro to both adefovir and lobucavir.

It is inherently obvious that resistance is a function of several factors in HBV that are also important for HIV. The bottom line is the degree of reduction of viral load. Nothing, to date, is capable of lowering viral loads far enough as a single agent. Resistance to lobucavir and adefovir has not been seen yet in clinical specimens, but the numbers of treated patients are small. Perhaps their increased potencies over lamivudine will keep them from the funeral pyre of single agent treatment. BMS 200, 475 perhaps will be potent enough on its own to avoid the need for combination. It is clear that interferon and lamivudine (8 weeks lamivudine followed by combination) are no better (and may be worse) than either agent alone. Other combinations will come slowly. None have been tested to date, although limited plans are underway. Lamivudine needs to find itself a good drug for combination or it risks resistance rates that parallel its use as a single agent in HIV. Whether the potency of the drug or its combination will determine treatments of

the future is unclear. For now, the hepatologists are just beginning to address long-term or life-long drug administration as the obvious solution. Triggers for stopping are being identified, such as anti-HBe seroconversion, but this is risky as seroconversions can revert. On the lighter side, it would appear that a possible source of HBV infection in endemic areas is the common bedbug (*Cimex Lectularius L.*) found in beds and movie theater seats in the Phillipines, for example.

Alaskan investigators introduced alphafetoprotein screening (902) q 6 months with ultrasound on those above 15 mg/mL for native patients with HBV. They increased five-year survival from hepatocellular carcinoma (HCC) from 0% to 45% using this paradigm. The problem with AFP is its relatively poor positive predictive value. CT scan appears more sensitive than ultrasound in detecting HCC.

There are new hepatitis viruses, too. Hepatitis G is still being studied and its vertical transmission pathway idenitifed. Parvovirus can cause an acute fulminant hepatitis that is rarely fatal, fully reversible, and should not be transplanted. Transfusion-transmitted virus (TTV) is a newly discovered DNA virus (*Biochem Biophys Res Comm* 1997;241:92) that has four distinct serotypes identified so far. Every study of this agent suggested that no significant liver disease results from it, much like HGV. The role for these viruses as possible cofactors continues to be debated and studied.

HIV-HCV coinfected patients do significantly worse than HCV patients without HIV. Alcohol abuse continues to be a significant cofactor for HIV and for all HCV patients. Be careful of hepatotoxicity in HIV-infected patients on HAART. Coinfections with HCV and/or HBV are common and may complicate therapy. Certain protease inhibitors were again found to be a problem here, associated with cholestasis, especially in coinfected patients. Some investigators did not see a correlation with protease inhibitors and disease severity. Others found that protease inhibitors improved liver function as a secondary effect of reducing HIV loads. Interferon alone does not induce a long-term benefit in HIV-coinfected patients, regardless of dose. Lamivudine does lower HBV DNA in patients coinfected with HBV, but resistance is common in this group. It appears safe to combine HAART with ribavirin and interferon without altering HIV load, despite ribavirin's potential for antagonism with some antiretrovirals. Patients with CD4 counts of more than 300 appear to respond to therapy as controls in a preliminary study of interferon alone. HCV is also a significant cofactor in morbidity and mortality of kidney transplant patients. Severe cholestatic hepatitis was associated with genotype 1. Coinfection with hepatitis A virus was suggested to carry a 35% mortality rate in HCV-infected individuals recently (*N Engl J Med* 1998;338:286). This was not confirmed in a Swiss study of more than 5000 patients, although there would be little reason not to immunize HCV-infected patients against both HBV and HAV, if indicated.

In summary, combination therapy appears to be the treatment of choice for HCV. The situation still requires careful patient selection and counseling. Not all patients will want to be treated. Most will want treatment regardless of reassurance about the low overall risk of death from liver disease in patients exposed to HCV, because prognosis is often not predictable and treatment may be more effective in advance of fibrosis. Many will suffer fatigue and depression and, for many, antivirals will not change that reality. Much of our disease management approach is based on studies dating back two decades when interferon alpha was used alone and disease was measured by the ALT response. It is important to distinguish the changing rules in assessing treatment studies from the past. ❖

Suggested Reading

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Which of the following is correct?

a. Patients who do not respond completely by six months of therapy with Interferon alpha plus ribavirin are unlikely to benefit from continued treatment.
b. Ribavirin antagonizes the effect of interferon alpha in the treatment of HCV infection.
c. Patients infected with genotype 1 of HCV infection respond more often and more rapidly to interferon alpha than those infected with other genotypes.

In Future Issues:

Using Hydrocortisone to Treat Chronic Fatigue Syndrome

UPDATES

By Carol A. Kemper, MD

Larium or Lamasil?

Source: Lobel HO, et al. *JAMA* 1998;280:1483.

This letter to the editor describes three cases of drug overdose with antimalarials, two of which resulted from dispensing errors for patients prescribed terbenafine (Lamasil) for onychomyosis. The first patient mistakenly received mefloquine 250 mg daily for three weeks, and then 2-3 times weekly for six months. He became increasingly weak, depressed, disoriented, and developed parathesias for three months before the error was discovered. He had not fully recovered one year later. The second patient similarly received mefloquine 250 mg daily instead of Lamasil. Within 10 days, she developed ataxia, confusion, speech impairment, and high-frequency hearing loss. She continued to receive the incorrect drug for a total of 61 days before the error was detected. Only hearing loss remained one year later.

The third case, which was much more frightening, involved a patient in a California hospital with *Plasmodium vivax* infection. She received 1250 mg of mefloquine on day 1, and 1260 mg of primaquine on day 2, at which time she became acutely jaundiced. She continued to receive primaquine 15 mg per day for five days. She developed acute hepatic necrosis, and was temporarily placed on the liver transplant list, but fortunately recovered.

In contrast to mefloquine, which has a high toxicity margin, primaquine has a fairly narrow margin of toxicity. The usual adult dose is 15-30 mg daily, but the probable lethal oral dose is 5-50 mg/kg (about 350-3500 mg for this patient). Not only does the treatment of malaria require expert knowledge (or advice), but these cases demonstrate why it's better to write prescriptions using the generic name of drugs in most cases. We should all be aware of the potential for confusion of Larium and Lamasil. ■

Hepatitis A Vaccine in HIV-Infection

Source: Orenstein R, Stewart M. 36th IDSA, Denver, November 12-15, 1998; Abstract 411.

Orenstein and colleagues examined the cost-effectiveness of three strategies for administration of hepatitis A vaccine in HIV-infected patients. They based their calculations on the seroprevalence rates of their patients at the VA Medical Center in Richmond, Va., 25% of whom were HAV IgG seropositive, 43% were HCV seropositive, and 32% both. The cost of two doses of Hepatitis A vaccine was $50 and that of HAV serology was $10.

The most cost-effective strategy ($22.45 per pt.) involved vaccinating only those HCV seropositive patients who were also HAV negative. In contrast, screening for HAV IgG and vaccination of all seronegatives cost $57.25 per patient, and no screening and vaccination of all subjects cost $63 per pt.

The first approach is based on recent reports that acute HAV infection is more severe in patients with chronic liver disease due to HCV infection. However, this strategy does not account for the cost of HCV-screening, nor the cost of missed work, clinic visits, additional laboratory costs, and possible hospitalization, or the confusion generated by acute HAV infection in an HIV-infected individual receiving multiple, potentially hepatotoxic, medications.

The U.S. Public Health Service recommends Hepatitis A vaccination for individuals at risk for HAV infection. Not only are HIV-infected patients frequent travelers, but sexually active gay men are at risk for acute HAV infection. Hepatitis A vaccination should be offered to all HIV-infected individuals who are sexually active gay men, who work in the food or health care industry, travel to developing countries, or who have chronic liver disease, or chronic Hepatitis B or C infection—which, after examining the list, seems pretty inclusive. ■

Different Diet, Less Gas?

Source: King TS, et al. *Lancet* 1998;352:1187.

King and associates examined whether colonic malfermentation could be a factor in the pathogenesis of Irritable Bowel Syndrome (IBS). Six female IBS patients and six female controls were enrolled in a randomized, cross-over study in which subjects received either a standard diet (containing the usual Western foods) or an elimination diet for two weeks, followed by the alternate diet for two weeks after a two-week washout period. The elimination diet included fish and meat, but not beef, soy products replaced dairy products, and cereals other than rice were prohibited. There were also restrictions on yeast, citrus, caffeine, and tap water.

Toward the end of each two-week diet, fecal excretion of fat, nitrogen, starch, and non-starch polysaccharide was measured, along with a 24-hour indirect calorimetry.

On the standard diet, colonic gas production of hydrogen was two times higher in IBS patients than controls, and excretion of hydrogen plus methane was nearly four times higher. While both IBS and control subjects had reduced gas production, especially of hydrogen, while receiving the elimination diet, the IBS patients had near-normalization of their gas excretion patterns. This was associated with significant improvement in their gastrointestinal symptoms. King et al speculated that the elimination diet favorably alters the activity of certain bacteria, thereby decreasing symptoms of IBS. ■