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Adefovir Dipivoxil Treatment of Chronic Hepatitis Due to HBV Infection

ABSTRACTS & COMMENTARY

Synopsis: *Adefovir dipivoxil, 10 mg p.o. daily, is safe and effective in the treatment of chronic hepatitis due to HBV, regardless of the presence or absence of HBeAg, and it did not select resistant mutants after 48 weeks of administration.*

Sources: Marcellin P, et al. Adefovir dipivoxil for the treatment of hepatitis B antigen-positive chronic hepatitis B. *N Engl J Med*. 2003;348:808-816; Hadziyannis SJ, et al. Adefovir dipivoxil for the treatment of hepatitis B e antigen-negative chronic hepatitis B. *N Engl J Med*. 2003;348:800-807.

Marcellin and colleagues randomized 595 patients from 78 centers in North America, Europe, Australia, and Southeast Asia with HBeAg-positive chronic hepatitis to receive adefovir dipivoxil in 1 of 2 doses (10 mg or 30 mg daily) or placebo in a double-blind trial. Histologic improvement at 48 weeks was found in 53%, 59%, and 25%, respectively, and log-transformed HBV DNA concentration per mL of plasma decreased by 3.52, 4.76, and 0.55, respectively ($P < .001$ for both comparisons with placebo). No HBV polymerase mutations associated with adefovir resistance were identified. While the 10-mg dose of adefovir was associated with a safety profile similar to that of placebo, the higher dose was associated with an increased risk of adverse events. Of note was a mean increase in serum creatinine of 0.2 mg/dL in the recipients of 30-mg adefovir daily.

Hadziyannis and colleagues at 32 sites in Canada, Europe, Asia, and the Middle East randomized 185 patients with hepatitis B e antigen (HBeAg)-negative chronic hepatitis in a 2:1 ratio to receive either adefovir dipivoxil (10 mg q.d.) or placebo in a double-blind study. Among those with liver biopsies, improvement in hepatic histology at 48 weeks was observed in 64% of adefovir recipients and 33% of placebo recipients ($P < .001$). The log-transformed median decreases in plasma HBV DNA level were 3.91 and 1.35 ($P < .001$), respectively, while the ALT levels normalized in 72% and 29% ($P <$

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THOMSON AMERICAN HEALTH CONSULTANTS

INSIDE

0.001). Mutations in HBV polymerase associated with adefovir resistance were not detected. Adefovir was well tolerated.

COMMENT BY STAN DERESINSKI, MD, FACP

There are now 3 FDA-approved medications for the treatment of chronic hepatitis due to HBV infection: interferon alpha, lamivudine, and adefovir. Tenofovir, approved for the treatment of HIV infection, also has significant activity against HBV. Adefovir dipivoxil is a prodrug of adefovir, a nucleotide analog of adenosine monophosphate that acts as an inhibitor of HBV DNA polymerase.

Interferon alpha is poorly tolerated and has been increasingly supplanted by lamivudine in the treatment of this infection. While lamivudine therapy has a favorable safety profile, its use is associated with selection of resistant mutants in approximately one-third of patients after a year of therapy. Adefovir was very well tolerated at the 10-mg daily dose in both these trials, but the 30-mg dose was associated with modest increases in serum creatinine and at least 1 case of a Fanconi-like syndrome, toxicities that were anticipated as the consequence of the experience with higher-dose adefovir in HIV infection. At the same time, no mutations associated with tenofovir resistance were detected in either of these studies after 48 weeks of therapy.

In these studies, adefovir therapy was associated with improvement in liver histology and an approximately 4 $\log_{10}$ decrease in HBV DNA in both HBeAg-positive and -negative chronic hepatitis. The efficacy, safety, and lack of emergence of resistance make adefovir an excellent choice in the treatment of chronic hepatitis due to HBV infection. The next logical step, the use of tenofovir and lamivudine in combination, is being currently evaluated. ■

Infectious Disease Alert, ISSN 0739-7348, is published twice monthly by Thomson American Health Consultants, 3525 Piedmont Rd., NE, Bldg. 6, Suite 400, Atlanta, GA 30305.

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GST Registration Number: R128870672.
Periodicals postage paid at Atlanta, GA.
POSTMASTER: Send address changes to ***Infectious Disease Alert,*** P.O. Box 740059, Atlanta, GA 30374.

Back issues: $20.
Missing issues will be fulfilled by customer service free of charge when contacted within one month of the missing issue's date.

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More Help with Sepsis from Biologics

ABSTRACTS & COMMENTARY

Synopsis: *rhIL-11 given orally to neutropenic rats experimentally infected with* Pseudomonas aeruginosa *appears to preserve the integrity of gut epithelia while resulting in fewer pathologic changes, lower levels of endotoxin and numbers of bacteria in the tissues, and longer survival. Recombinant human interleukin 11 (rhIL-11) administration was associated with a reduction in a variety of infectious complications, including bacterium due to Gram-negative bacilli originating from the gut among patients given intensive chemotherapy for hematologic malignancies.*

Sources: Ellis M, et al. Recombinant human interleukin-11 and bacterial infection in patients with haemotological malignant disease undergoing chemotherapy. *Lancet*. 2003;361:275-280; Opal SM, et al. Orally administered recombinant human interleukin-11 is protective in experimental neutropenic sepsis. *J Infect Dis*. 2003;187:70-76.

INTERLEUKIN-11 IS A PLEIOTROPIC CYTOKINE WITH several targets in addition to the main one, the megakaryocyte. These include, surprisingly, the enterocyte. For example, rhIL-11 is known to protect hamsters from mucositis induced by 5-fluorouracil and radiation therapy.[1] It has other broad immunoprotective capabilities, primarily in downregulating proinflammatory

responses. Furthermore, Opal and colleagues showed that rhIL-11 protects rats against experimental sepsis due to *Pseudomonas aeruginosa*, and when oral human IL-11 is given to the animals, systemic levels of endotoxin were reduced and the animals maintained their mucosal mass. Moreover, in both hamsters and rats, weight loss was reduced by rhIL-11. Interestingly, TNF-alpha and interferon-gamma messenger RNA were also reduced in enterocytes, suggesting that rhIL-11 preserves epithelial cell integrity and providing a rationale for its use as an adjunct to treating or ameliorating sepsis due to enteric bacteria.

Investigators at Tawan Hospital in Al-Ain, United Arab Emirates, in collaboration with Swedish and Welsh colleagues, studied 40 patients undergoing intensive chemotherapy for hematologic malignancies (mainly AML and ALL). Patients were randomly assigned to receive 50 μg/kg rhIL-11 or a matching saline placebo subcutaneously daily from the start of chemotherapy for as long as granulocytes remained below 0.5×10^9/L or for 21 days—whichever was longer. Fever was managed by giving empirical therapy, and G-CSF was given to two-thirds of patients because of severe neutropenia (granulocytes $< 0.1 \times 10^9$/L for more than 10 days) There were 20 patients in each group, the average age was 36, and the men outnumbered the women 3 to 1.

rhIL-11 was given for an average of 21.5 days and the placebo for an average of 24 days. The main outcome was a reduction in bacteremia, and other outcomes included the time to occurrence of first bacteremia, the distribution of bacteria among patients, febrile events, and mucosal damage. On both counts, rhIL-11 succeeded in outperforming a placebo. Thirteen patients in the placebo group experienced bacteremia involving 20 different species, of which 15 were Gram-negative bacilli compared with only 5 patients in the treatment group involving 6 species, of which 4 were Gram-negative bacilli. Bacteremia also occurred later in the rhIL-11 group. Significantly fewer patients given rhIL-11 developed pneumonia and enterocolitis (10% and 20%, respectively) than in the placebo group (45% and 40%, respectively). Hypotension associated with sepsis also affected only 2 patients given the rhIL-10 compared with 7 given placebo. Logistic regression indicated that treatment with rhIL-11 was the only factor to independently reduce the risk of enteric bacteremia ($P = .04$) .

The C-reactive protein concentration was higher in rhIL-11 patients before and during neutropenia, but the rate of oral mucositis was significantly reduced. As might be expected, the rhIL-11 group also recovered the platelet count faster. The urinary lactulose-mannitol ratio was used to assess gastrointestinal permeability and was more often normal for patients given rhIL-11 (14/18, or 78%) than for those given the placebo (9/20, or 40%). Two patients died in each group: two in the treatment group secondary to nonbacterial causes and 1 in the treatment group that may have died as a result of *Clostridium difficile* enterocolitis. Apart from peripheral edema that affected 6 patients given rhrhIL-11 and 2 given the placebo, the side effects were infrequent, mild, and considered manageable.

COMMENT BY J. PETER DONNELLY, PhD, AND JOSEPH F. JOHN, Jr., MD

The race continues to bolster the antimicrobial therapy of sepsis. Clinicians in the United States have of late been wrestling with the role that drotrecogin alpha (Xigris™) should play in managing sepsis, and usage does seem to be increasing, particularly in intensive care units. We are currently awaiting more information about its efficacy and toxicity in phase 4 trials.

The approach taken by Ellis and colleagues was motivated by the long-held belief that the gut is the origin of Gram-negative bacillary infection in neutropenic patients and that its integrity is damaged by cytoreductive chemotherapy. Hence, they designed, in essence, a proof-of-concept study to see whether treatment with rhIL-11 would reduce Gram-negative sepsis and , if so, if it was associated with preservation of the mucosal integrity of the gastrointestinal tract.

The study was carried out in a hospital in the UAE in collaboration with Swedish and Welsh scientists. Although the number of patients was small, the outcomes were virtually all polarized in favor of rhIL-11. One might quibble over whether bacteria such as *Fusobacterium* species and *Stenotrophomonas maltophilia* are enteric in origin, but the fact remains that if the reduction in bacteremia is shown to be as large as found in this study, then there is an enormous potential benefit for these patients and not just in terms of Gram-negative sepsis. The rates of pneumonia were also significantly lower after treatment with rhIL-11. Hence, the patients benefited from rhIL-11 by experiencing fewer infectious complications all around.

Of particular interest was the apparent preservation of gut integrity, suggesting a strategy of stabilizing enterocyte integrity to reduce transposition of bacteria across the intestinal mucosa. If this is true, then one could extend this to other patients such as those in the ICU because of trauma or surgery. Furthermore, unlike some other biological agents being used in clinical practice like the interferons, the rate of fever in the rhIL-11 group was actually lower than that in the placebo group, although CRP levels were higher.

The side effects of almost 3 weeks of subcutaneous treatment were not considered important, although the occurrence of peripheral edema might well give cause for concern. The fact that that gut mucosa was preserved appears to complete the picture and proves the earlier observations in hamsters were correct.

Just as this clinical paper appeared, Opal et al extended their original observations that rhIL-11 and rhG-CSF improved the outcome of experimentally induced Gram-negative sepsis in neutropenic rats[2] by exploring an oral form of rhIL-11 in the same model. This treatment reduced the expression of genes for TNF-α and interferon-γ in enterocytes, suggesting that the compound may preserve epithelial cell integrity during chemotherapy. Taken together, it would appear that rhIL-11 acts directly on the gut mucosa. This is very exciting, indeed, since rhIL-11 in an oral form offers an approach to preventing or at least ameliorating the gut toxicity induced by the intensive cytoreductive chemotherapy used to treat hematologic malignancies and to prepare for stem cell transplants. A formal blinded, placebo-controlled trial with sufficient power that showed gut integrity to be maintained and infectious complications to be reduced would make a major contribution to the well-being of thousands of patients by consigning mucositis in its oral and gut manifestations to history, protecting patients against the ravages of Gram-negative sepsis without having to resort to antimicrobial agents for prophylaxis, and helping them maintain their weight and perhaps even continue eating and drinking normally. What more can one ask? ■

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Avian Influenza Redux

ABSTRACT & COMMENTARY

Synopsis: *Avian influenza virus has reemerged in Hong Kong and, independently, in The Netherlands, where it has caused conjunctivitis in poultry workers.*

Source: Promed archives at http://www.promedmail.org.

A 33-YEAR-OLD HONG KONG RESIDENT DEVELOPED respiratory symptoms on February 7, 2002, while visiting Fujian Province, China, with his family. He returned to Hong Kong the following day and was admitted to a hospital on February 11, where he died 6 days later. The man's 9-year-old son, who also became ill while in Fujian, was admitted to the Hong Kong hospital on February 12 with pneumonia but survived. The boy's 8-year-old sister died while in Fujian on February 4. The mother is recovering from a respiratory tract infection. Influenza A virus (H5N1) was isolated from nasopharyngeal isolates from the boy and from postmortem specimens of the father. The etiology of the mother's illness was thought to have been parainfluenza virus infection, while the etiology of the girl's death has not yet been determined.

At least 65 poultry workers in The Netherlands, where an outbreak of influenza A (H7N7) is affecting poultry plants, have developed infection due to this virus. Most patients had conjunctivitis as the main manifestation of infection. There has been 1 instance of human-to-human transmission identified. The viral strain is susceptible to oseltamivir, and it has been recommended that this drug be prophylactically administered to workers at affected sites.

COMMENT BY STAN DERESINSKI, MD, FACP

Eighteen people, 6 of whom died, were infected with avian influenza A virus (H5N1) in Hong Kong in 1997.[1] The etiologic pathogen in that outbreak is not, however, related to the current influenza A strain. Sequencing of the recently isolated virus has demonstrated it to be genetically distinct from the earlier strain.

Avian influenza A virus subtype H9N2 was isolated from 5 humans on mainland China in August 1998, and in March of 1999 influenza A virus (H9N2) was isolated from 2 children in Hong Kong with flu-like illnesses.[2]

While these infections caused a typical influenza-like illness, avian influenza may also cause conjunctivitis in humans, as illustrated by the experience in The Netherlands. This is not the first report of this phenomenon: An H7N7 influenza virus of avian origin was isolated from a woman with a self-limited conjunctivitis in 1996.

These viruses have limited capacity for human-to-human transmission. A major concern is the possibility that genetic reassortment could occur with emergence of a virus capable of spread through a human population immunologically naïve to the viral antigens.[3] ■

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3. Capua I, et al. The 1999-2000 avian influenza (H7N1) epidemic in Italy: Veterinary and human health implications. *Acta Trop*. 2002;83:7-11.

Tips on TIPS Infections

ABSTRACT & COMMENTARY

Synopsis: *Infection of transjugular intrahepatic shunt devices is caused by a variety of bacteria, mostly of gastrointestinal origin. Inability to remove the device without hepatic transplantation makes management of the infection difficult.*

Source: Armstrong PK, Macleod C. Infection of transjugular intrahepatic portosystemic shunt devices: Three cases and a review of the literature. *Clin Infect Dis*. 2003;36:407-412.

ARMSTRONG AND COLLEAGUES IN NEW SOUTH WALES identified 3 patients with infection of transjugular intrahepatic portosystemic shunt (TIPS) devices from among 154 patients who underwent 180 TIPS procedures. In addition, they identified 21 published cases meeting their diagnostic criteria, which required the presence of sustained bacteremia in the absence of an explanation other than TIPS infection.

Among the Gram-positive etiologic pathogens were *Staphylococcus aureus* (3), *Enterococcus faecalis* (8), *Streptococcus sanguis* (1), *Streptococcus bovis* (1), *Gemella morilorum* (1), and *Lactobacillus acidophilus* (2). Gram-negative infections were caused by *Escherichia coli* (5), *Pseudomonas aeruginosa* (2), *Klebsiella pneumoniae* (2), and 1 each of *Klebsiella oxytoca*, *Acinetobacter calcoaceticus*, *Citrobacter amalonaticus*, and *Bacteroides fragilis*. Two infections due to *Candida glabrata* and 1 to *Candida albicans* were identified. Four of the infections were polymicrobial.

The incubation period ranged from 1 to 1065 days, with most cases occurring more than 2 months after placement of the device. The majority had evidence of occlusive thrombosis or vegetation. The outcomes after antibiotic therapy were variable.

COMMENT BY STAN DERESISNKSI, MD, FACP

It is inevitable that we will encounter infections such as these given the increasing use of TIPS devices for the management of portal hypertension. Most are caused by organisms that are part of the gastrointestinal flora. However, an anaerobic pathogen (*B fragilis*) was isolated from only 1 of the cases described here. *Candida* was isolated from 3 patients.

The ability to eradicate the pathogen with antibiotic therapy alone is problematic. Removal of the TIPS is not, unfortunately, possible without liver transplantation. As a consequence, patients with relapse of infection after discontinuation of a prolonged course of bactericidal antibiotic therapy may require lifelong suppressive therapy.

Last month I saw a patient with a TIPS device in place who was being treated for his second relapse of *E faecalis* bacteremia. Evaluation to identify a source of infection other than the TIPS device, which included a transesophageal echocardiogram, was unrevealing. This patient will indefinitely receive lifelong antibiotic therapy in an attempt to prevent further relapse. ■

Reducing Ventilator-Associated Pneumonia Rates Through Staff Education

ABSTRACT & COMMENTARY

Synopsis: *A focused-education program was associated with a dramatic reduction in the incidence of ventilator-associated pneumonia.*

Source: Zack JE, et al. *Crit Care Med*. 2002;11:2407-2412.

THE PURPOSE OF THIS PRE- AND POSTINTERVENTION observation study was to evaluate the effect of an educational initiative on ventilator-associated pneumonia (VAP) rate. The educational program was directed toward respiratory therapists and critical care nurses. The patient population consisted of those developing VAP during a 2-year period. A multidisciplinary task force developed policies and an educational initiative to reduce VAP rates. The educational program consisted of a self-study module, lectures, and pre- and post-testing. The focus of the self-study module was coverage of general topics related to VAP and specific emphasis on risk reduction strategies. Successful completion of the program was required of all respiratory therapists and made available to critical care nurses on an elective basis. Posters related to VAP were posted throughout the ICU. The pre-intervention period occurred from October 1, 1999, to September 30, 2000, and the postintervention period occurred from October 1, 2000, until September 30, 2001. The diagnostic criteria for VAP were a modification of those established by the American College of Chest Physicians.

A total of 114 respiratory therapists completed the educational program. The average correct score on the exam increased from 80% to 91% ($P < 0.001$)

after completing the educational module, and the average score 6 months after implementing the intervention was 85%. The educational module was also completed by 146 critical care nurses, and their scores on the test increased from 81% to 91% ($P < 0.001$). During the 12-month period before the intervention, the VAP rate was 12.6 per 1000 ventilator days. Following the intervention, the VAP rate was 5.7 per 1000 ventilator days—a decrease of 57.6% ($P < 0.001$). The cost saving associated with this intervention was calculated to be at least $424,000. Zack and colleagues concluded that an educational program focused on respiratory therapists and critical care nurses resulted in significant reductions in VAP rate.

COMMENT BY DEAN R. HESS, PhD, RRT

Nosocomial infections are an important cause of morbidity and mortality. Pneumonia is the most common nosocomial infection, and 86% of nosocomial pneumonia cases are associated with mechanical ventilation. Respiratory therapists and intensive care nurses are intimately involved in the care of mechanically ventilated patients and are, thus, uniquely positioned to affect VAP rates. Significant opportunities exist to improve VAP prevention practices.[1-3] These include decreasing the frequency of ventilator circuit changes, increasing the use of noninvasive ventilation, and elevation of the head of the bed.

Despite considerable evidence that has emerged in recent years, approaches to the prevention of VAP remain archaic in many intensive care units. Although there is considerable evidence of the benefit of the semi-recumbent position for the prevention of VAP, I frequently observe mechanically ventilated patients who are not positioned accordingly. Despite considerable evidence[4] that changing ventilator circuits and in-line suction catheters at regular intervals does *not* decrease VAP rate (and a meta-analysis suggests that this might actually *increase* VAP rate), the practice of changing circuits at regular intervals continues in many hospitals. I know of instances where infection control departments blocked the plans of respiratory care departments to implement the practice of as-needed ventilator circuit changes because adopting such a practice "does not make sense"! Unfortunately, what makes sense in the minds of some (dare I call this "expert" opinion?) still trumps high-level evidence in many hospitals. Despite evidence that it decreases intubation rate, increases survival, and decreases VAP rate, noninvasive ventilation in appropriately selected patients remains underused in many hospitals.

This study by Zack et al shows that an educational intervention directed primarily at respiratory therapists and critical care nurses can significantly reduce ventilator-associated pneumonia rates and associated costs. However, Zack et al have not reported whether this intervention affects other important outcomes such as antibiotic use, length of hospital stay, or mortality. In spite of these limitations, an education program such as the one described in this study should be considered—particularly for hospitals with a higher than expected ventilator-associated pneumonia rate. ■

Dr. Hess is Assistant Professor of Anesthesia at Harvard Medical School and Assistant Directory of Respiratory Care at Massachusetts General Hospital.

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Editor's Note: *For the latest CDC recommendations, see CDC Draft Guidelines for Prevention of Healthcare-Associated Pneumonia, 2002. www.cdc.gov.*

Rift in the Arabian Peninsula

ABSTRACT & COMMENTARY

Synopsis: *The first outbreak of rift valley fever outside of Africa was associated with a high frequency of severe hepatic involvement and acute renal failure.*

Source: Al-Hazmi M, et al. Endemic rift valley fever in Saudi Arabia: A clinical study of severe illness in humans. *Clin Infect Dis*. 2003;36:245-252.

Al-Hazmi and colleagues report their experience with 165 patients with rift valley fever admitted to a single hospital in southwestern Saudi Arabia

from September through November 2000. Prior direct contact with either infected and sick relatives or with sick, aborted, or dead animals was reported by 60%. Eighty percent reported frequent mosquito bites, and 13% frequently ingested raw milk.

Nausea or vomiting was reported by 92% of the patients, and 74% complained of fever and/or chills. Forty-six percent had abdominal pain, 43% had diarrhea, 41% had headache, 40% had myalgia, and 30% had symptoms referable to the central nervous system. Seventeen percent had hemorrhagic manifestations, and 11% were jaundiced. Hepatomegaly and splenomegaly were detected in 13% and 12%, respectively.

Ninety percent had AST levels > 3 times the upper limit of normal, and 75% of patients had hepatic failure. Renal dysfunction was present on admission in 55%, and one-fifth of the 165 patients required hemodialysis. Retinitis was detected in 10% during hospitalization and was bilateral in the majority. Three of the 16 with retinitis had permanent vision loss. The in-hospital mortality was 34%.

COMMENT BY STAN DERESINSKI, MD, FACP

Rift valley fever is caused by a Phlebovirus that is usually transmitted by the bite of infected *Aedes* and *Culex* mosquitoes, although it may also be acquired by contact with infected body fluids of animals. Symptomatic infection occurs after an incubation period of 3-7 days. Fever, headache, arthralgias, myalgias, and photophobia are the usual initial symptoms. Most cases are self-limited, but, as in the Saudi outbreak, the first identified outside of Africa, the infection may be severe and even fatal. In this outbreak, hepatic involvement was a common element of severe infection.

Rift valley virus is one of many causes of hemorrhagic fever syndrome which, in Saudi Arabia, must primarily be distinguished from Crimean-Congo hemorrhagic fever. Death may also be associated with acute renal failure and with encephalitis, as well as hepatic failure. A characteristic finding, although occurring at a relatively low frequency, is that of macular and perimacular retinitis, a manifestation of a vasculitic process that may lead to permanent blindness. Ribavirin therapy has been reported to be effective in animal models of infection, but its efficacy in human infection is unknown. An inactivated RVF vaccine has been reported to be safe and immunogenic in humans. ■

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16. Which of the following is correct with regard to infections of transjugular intrahepatic shunt (TIPS) devices?

a. The optimal management involves immediate removal and replacement of the device.
b. The etiologic agents are primarily organisms likely to have originated in the gastrointestinal tract.
c. Most cases become evident within the first week after placement of the device.
d. Short duration antibiotic therapy is invariably successful in eradication of the pathogen.

17. Which of the following is correct with regard to human infections with avian influenza A virus strains of avian origin?

a. The recent outbreaks in China and The Netherlands were caused by identical strains of the virus.
b. The strain of avian influenza virus causing the recent cases in China is genetically identical to that of an outbreak in 1977 in Hong Kong.
c. They may cause conjunctivitis in humans.

18. Which of the following is correct?

a. Adefovir is a nucleotide analog.
b. Adefovir is a nucleoside analog.
c. Adefovir is ineffective in patients with chronic hepatitis due to HBeAg-negative HBV infection.
d. Adefovir administration in patients with chronic hepatitis due to HBV infection is associated with the frequent emergence of resistance-associated mutations in the first 48 weeks of therapy.

Answers: 16(b); 17(c); 18(a)

In Future Issues:

SARS

UPDATES

By Carol A. Kemper, MD, FACP

Chloramphenicol-Tainted Honey

Source: ProMED-mail. July 13, 2002. promedmail@promedmail.org.

IMPORTED HONEY IS BECOMING big business. With Third World labor costs being substantially lower, imported honey prices are driving down the costs of United States-produced honey to the lowest levels in years, potentially affecting the numbers of apiarists (with no doubt some negative effect on the numbers of hives farmed out to fields and orchards).

Streptomycin- and chloramphenicol-tainted honey imported from China and Thailand began appearing sometime last year, prompting the European Union and Canada to ban honey imports from China last spring. Nonetheless, a jar of chloramphenicol-contaminated honey was found in a grocery store in Louisiana last summer.

How the honey was discovered there was not revealed, but the honey was tracked back to a producer in Thailand, where 2 55-gallon drums of honey were found to be contaminated with low levels of chloramphenicol. How the antibiotic got there is anyone's guess, but chloramphenicol has been used in animal feed in some countries for years.

Although the levels were extremely low (5.46 parts per billion) and are not likely to promote resistant or allergic reactions at that level, idiosyncratic reactions, such as bone marrow suppression, are not dose dependent and can occur with very minimal exposure to the drug.

As a result, the FDA has a zero-tolerance level for chloramphenicol in food products. Because honey is used in so many food products, such as cereals, snacks, and granola bars, tainted honey could have a wide impact. The United States has moved to ban all honey imports from China and Thailand unless they have first been sampled and tested. ■

Problems with Britain's Pet Scheme

Source: Pro-MED mail. March 8, 2003. promedmail@promedmail.org.

THE REVISED BRITISH PET TRAVEL Scheme (Kemper C. *Infectious Disease Alert*. 2003;10:80), which eliminated the need for quarantine of pet cats and dogs entering Great Britain from designated host countries, has come under fire from veterinarian researchers.

Recent data collected from 67 dogs and 3 cats entering Great Britain from April 2001 to July 2002 raise concerns that rabies may not be the only reason to consider quarantine of animals. All of the animals had entered the country under the new rules, although 14 dogs and 1 cat required quarantine because of their country of origin or inadequate clearance.

All of the animals were screened for babesiosis, leishmania, and ehrlichiosis. None of the cats showed evidence of infection. However, 24 (36%) of the dogs were infected with one or more pathogen, including 17 dogs that were not quarantined. Babesiosis was the most common pathogen identified, occurring in 10 dogs. Fortunately, dog strains of *Babesia* do not infect humans, although they can infect other dogs. Six dogs had ehrlichiosis (5 required quarantine), which can potentially infect humans. And at least 4 dogs from Spain had leishmania, which requires the appropriate sandfly vector for transmission, but nonetheless poses a risk. More intensive surveillance has been proposed. ■