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Conference Summaries of ICAAC 1999 and IDSA 1999: Part II

CONFERENCE COVERAGE

Editor's Note: *The following summaries represent a selection of papers presented at the 39th Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC), held September 26-29, 1999, in San Francisco and the 37th Annual Meeting of the Infectious Disease Society of America (IDSA), held November 18-21, 1999, in Philadelphia. It is important to recognize that many of these summaries are extracted only from the published abstract and it is possible that some of the material presented at the conference may have differed. The ICAAC abstracts are available on the American Society of Microbiology Web site at: http://www.asmusa.org. The IDSA abstracts can be seen in Clin Infect Dis 1999;29:959-1112. —Stan Deresinski, MD, FACP*

Complications of ART

Lactic Acidosis. There is increasing concern about the relationship of ART and lactic acidosis. Three patients receiving NRTIs and presenting with either weakness or nausea and vomiting had lactic acidosis. They were successfully treated with bicarbonate and riboflavin. (*IDSA #212.*)

The FDA reported it had been notified of 60 cases of lactic acidosis in patients receiving combination NRTIs as well as 46 who were receiving a single NRTI. Of the former group, 36 were receiving lamivudine/stavudine, nine didanosine/stavudine, seven each lamivudine/zidovudine and didanosine/zidovudine, and one each stavudine/zidovudine and zidovudine/zalcitabine. Presenting symptoms often included, in various combinations, nausea, vomiting, abdominal pain, dyspnea, and weakness. Among the 36 receiving lamivudine/stavudine, 20 (56%) of whom died, lactic acidosis was recognized a mean of 255 days after the start of therapy. There were 69% reported to have hepatic steatosis. Approximately 83% of the 36 were female and half of these were reported to be obese or to weigh

more than 175 pounds. (*ICAAC #1284.*)

Eleven patients with increased lactic acid levels were seen over 18 months in one French department, for an annual incidence of 0.84% for all patients receiving antiretroviral therapy and 1.56% for those receiving stavudine/didanosine. All 11 were receiving stavudine alone or in combination. Four had chronic hepatitis C virus infection, one had chronic hepatitis B infection, and one was obese. ART was discontinued in nine, riboflavin was administered to six, carnitine was administered to four; hyperlactatemia resolved in 10 of the 11. (*ICAAC #1285.*)

Ten patients receiving regimens, including stavudine and at least one other NRTI for a median of 10 months, presented primarily with nausea, abdominal pain, and distention, and with modest increases in lactate and AST levels. In eight, there was no decrease in serum bicarbonate or increase in anion gap. Five of six liver biopsies showed micro- and macrovesicular fat. Only one required hospitalization and none died; the median time to resolution of hyperlactatemia after discontinuation of NRTIs was 62 days. The estimated incidence in this clinic was approximately 15 per 1000 person-years. (*IDSA #348.*)

Lipodystrophy and Hyperlipidemia. Diminution of facial fat, quantified by MRI, correlates with the duration of protease inhibitor therapy. (*IDSA #324.*) Among patients receiving a protease inhibitor, lipodystrophy was detected in two of 46 (4.2%) of those also receiving zidovudine/lamivudine, 45 of 87 (51.7%) of those receiving stavudine/lamivudine, and 17 of 19 (89.4%) receiving stavudine/didanosine. There was no difference in the protease inhibitor used; indinavir was the most commonly administered. (*ICAAC #1303.*)

Ten patients who developed lipodystrophy while receiving stavudine/didanosine and a protease inhibitor had their NRTIs changed to zidovudine/lamivudine with improvement in anthropometrics and triglycerides through 24 weeks. (*ICAAC #1306.*)

Patients with undetectable viral loads on protease inhibitor-based HAART regimens who developed metabolic abnormalities and liposdystrophy had efavirenz substituted for their protease inhibitor. Triglycerides and cholesterol increased as did body weight, but visceral fat (by CT scan) decreased. Virological control was maintained. (*ICAAC #2064.*)

Recombinant human growth hormone (2-4 mg qod) reduced truncal obesity (as determined by bioelectrical impedance), but not breast size, in nine of 16 women with lipodystrophy. (*ICAAC #1305.*)

In START II, patients were randomized to receive indinavir together with either lamivudine/zidovudine or stavudine/didanosine; hypertriglyceridemia was more frequent in the latter group. (*IDSA #14.*) Replacing other protease inhibitor-containing regimens with salvage regimens containing ritonavir/saquinavir was associated with significant increases in serum lipids which were correlated with the dose of ritonavir administered. (*ICAAC #1290.*)

Seventeen patients intolerant to liquid ritonavir were switched to regimens containing nelfinavir or nelfinavir/saquinavir (sgc). All maintained undetectable viral loads. In addition, their mean triglyceride levels decreased from 4.42 to 2.62 mmol/L (P = 0.001) in both groups and GGT also significantly decreased.

A retrospective study found that administration of a HMG-CoA reductase inhibitor (statin) to patients receiving protease inhibitors reduced cholesterol levels a median of 17% and triglycerides 53%; normalization of levels was, however, infrequently achieved. One of 20 patients developed a marked increase in CK level. (*ICAAC #1297.*) Fenofibrate administration (200 mg with sup-

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per) was associated with a 72% decrease in serum triglyceride levels in 10 patients with hyperlipidemia on protease inhibitors. (*ICAAC #1294.*) Bezafibrate had similar effects. (*ICAAC #1296.*)

Miscellaneous Complications. Administration of calcium tablets (500 mg bid) to 15 patients with diarrhea while receiving nelfinavir was associated with complete resolution within 48 hours in 13 (87%) and improvement in the other two. (*ICAAC #1308.*)

A retrospective analysis of 165 patients treated with nelfinavir and 175 with indinavir found 15 (8.5%) new cases of hypertension developing among the former and 37 (22%) among the latter (P = 0.003). By multivariate analysis, only indinavir use was associated with the development of hypertension. (*ICAAC #1310.*)

While the overall incidence of osteonecrosis in one county HIV clinic (0.29%) was approximately 58-fold greater than in the general population, most of the increased risk was explainable by the presence of previously known factors, such as corticosteroid use and alcoholism. In particular, protease inhibitor use was as frequent in controls as in cases. (*ICAAC #1311.*) Another clinic reported a 1.3% incidence of osteonecrosis; eight of 10 had risk factors other than HIV infection or protease inhibitor use. (*ICAAC #1312.*)

In a randomized trial involving NRTI experienced, but protease inhibitor-naïve patients, a comparison of the use of 60 mg and 120 mg adefovir dipivoxil daily found that, although the virological responses were similar, the lower dose was associated with significant reduction in toxicity. (*ICAAC #1976.*)

Immunology, Immune Reconstitution, and Immunotherapy

Immune Reconstitution. Immune reconstitution after HAART appears to be incomplete in some patients. Fifty-five of 162 patients anergic prior to initiation of HAART developed at least one positive skin test 6-12 months after its initiation. However, none of 71 patients previously known to have had a positive PPD or tuberculosis developed a positive skin test after HAART, despite the fact that 29.1% were no longer anergic to other antigens. (*ICAAC #1825.*) Humoral immunity is enhanced by successful HAART. Patients with asymptomatic CMV viremia had an increase in anti-gB geometric mean titer (gB is the major neutralizing target in CMV) from 1:117 to 1:1644 (P < 0.01) after institution of HAART, while controls did not. All HAART recipients became CMV DNA negative in blood. There was no effect on anti-Gag (pr55) antibody titers, however. (*ICAAC #1826.*) Similarly, eight of 11 children with a history of varicella zoster infection who were seronegative for this virus seroconverted after introduction of HAART. (*IDSA #423.*)

HAART may also be associated with improved capacity of phagocytic cells. Spontaneous neutrophil apoptosis is significantly decreased ex vivo or in vitro by exposure to one of several protease inhibitors. (*ICAAC #1830.*) Administration of a nelfinavir-containing HAART regimen to 10 patients was associated with a priming effect on neutrophil respiratory burst. (*ICAAC #1831.*)

Immune Enhancement Disease. Herpes zoster may be one of the manifestations seen after successful HAART. Examination of a cohort of 70 children begun on antiretroviral therapy with at least three drugs found that five developed herpes zoster after a mean of 4.1 months at a time of control of viral replication and improved immunological status. In addition, one who had an undetectable (< 50 copies/mL) viral load and CD4 of 13.5% developed life-threatening varicella pneumonia despite the administration of VZIG. (*IDSA #666.*)

A case control study of 12 cases of herpes zoster occurring within 17 weeks of starting HAART found, in a multivariate analysis, that the only identified risk factor was an observed increase in percentage of CD8 cells. The incidence of zoster in protease inhibitor-treated patients was 8.9 episodes per 10 patient-years. (*IDSA #674.*)

Immunotherapy. GM-CSF has a variety of potentially beneficial effects in HIV-infected patients (*AIDS* 1999;13:633-643). Three hundred nine patients with CD4 less than 50/mm^3 or less than 100/mm^3 plus and AIDS-defining illness without neutropenia and on stable ART and OI prophylaxis were randomized to receive thrice-weekly GM-CSF or placebo subcutaneously for 24 weeks. GM-CSF recipients had fewer overall infections or death (67% vs 78%; P = 0.03) and delayed time to first infection or death (97 days vs 56 days; P = 0.04). GM-CSF administration was associated with significant increases in neutrophil count and in CD4 T cell count. Patients receiving GM-CSF also had a longer duration of viral suppression and, among those with viral load less than 30,000 copies/mL at baseline, required fewer changes in ART. (*ICAAC #693.*)

The putative mechanism by which GM-CSF might reduce viral load is downregulation of chemokine receptors on monocytes and macrophages. In like fashion, thalidomide was found to inhibit CXCR4 and CCR5 expression on CD4 T cells resulting from induction by mycobacterial antigens in vitro. (*ICAAC #1838.*)

Interleukin-2 was absorbed at t1/2 of 50 minutes after subcutaneous administration of 250,000 U/m^2 and

detectable levels persisted in serum for more than 14 hours, having reached a peak plasma concentration of 25pM at three hours. (*ICAAC #1828.*) In contrast to initial findings at the NIH with single infusions, no effect on viral load was observed in patients given interleukin-10 for four weeks. (*IDSA #319.*)

Complications of HIV Infection

Bacterial Infection. While HIV-infected patients (mean CD4 count 244 cells/mm^3) responded to pneumococcal vaccine as well as non-HIV-infected controls when antibody was measured by ELISA, they had a poorer response when opsonizing antibodies were compared. (*ICAAC #1824.*)

Kaposi's Sarcoma. An HIV-infected patient with protein-losing enteropathy proved to have Kaposi's sarcoma of the gastrointestinal tract as the cause. (*IDSA #205.*) Treatment of Kaposi's sarcoma with liposomal doxorubicin was associated with clearance of HHV-8 from blood in 15 of 16 patients positive at baseline. (*ICAAC #112.*)

Mycoses. Multivariate analysis found that working with soil mixed with bird and bat droppings was a significant risk factor for the development of histoplasmosis in HIV-infected patients. The receipt of any antiretroviral therapy or of fluconazole were independently associated with a decreased risk of this fungal infection. (*IDSA #399.*)

Urine histoplasma antigen was detected in all 11 HIV-infected patients with disseminated histoplasmosis tested as well as in four of six non-HIV patients with disseminated infection and one of four without disseminated infection. Blood cultures were positive in 12 of 22 (55%) of HIV patients and six of nine of non-HIV patients with disseminated histoplasmosis; bone marrow was positive in, respectively, seven of 22 (33%) and one of nine (11%). (*IDSA #263.*)

Two hundred sixty-seven patients with cryptococcal meningitis were randomized to receive, for 14-21 days, amphotericin B (0.7 mg/kg/d), or one of two doses of liposomal amphotericin B (3 mg/kg/d or 6 mg/kg/d). This was followed by fluconazole 400 mg/d in each group for a total of 10 weeks of therapy. There was no difference in outcomes between the groups, but the use of liposomal amphotericin was associated with significantly fewer infusion-related adverse events and significantly less nephrotoxicity. (*ICAAC #1161.*)

A case of protracted hypoglycemia in an AIDS patient was attributed to PCP prophylaxis with trimethoprim/sulamethoxazole. (*IDSA #237.*)

Six hundred seven patients whose CD4 count had increased to more than 200 cells/mm in response to HAART were randomized to continue or discontinue PCP prophylaxis. No episodes of PCP occurred in either arm during a median follow-up of 6.7 months and a total of 340 person-years. (*ICAAC #1165.*)

Bacterial Infection. Patients with MAC bacteremia were randomized to receive, together with ethambutol, azithromycin 250 mg po qd, azithromycin 600mg po qd, or clarithromyicn 500 mg po bid. Interim analysis found 250 mg daily azithromycin to be inferior and this arm was dropped from the study. There was no significant difference in outcomes between those receiving the higher dose of azithromycin and those receiving clarithromycin. By 24 weeks, at least one negative blood culture had been achieved in 59% of 68 higher dose azithromycin recipients and 61% of 57 clarithromycin recipients. (*ICAAC #1163.*)

Recurrence of "disseminated" MAC infection occurred in four patients despite their receipt of HAART, clarithromycin, and ethambutol. Two had positive lymph node cultures and one each had positive blood and small bowel cultures. At the time of recurrence, their mean CD4 cell count was 81/mL (range, 57-132/mL); each had an undetectable viral load. (*IDSA #396.*)

Antiretroviral therapy and macrolide prophylaxis were each protective against pneumococcal disease, as was vaccination at CD4 count more than 500 cells/mL. However, vaccination at lower CD4 count was not protective. (*IDSA #377.*) However, a prospective study of the development of macrolide resistance of oropharyngeal flora of patients receiving MAC prophylaxis with either clarithromycin (500 mg po bid) or azithromycin (1200 mg po weekly) was terminated after all 23 patients who reached 12 weeks developed resistant flora (MIC > 256 mcg/mL). (*ICAAC #1164.*)

Confirming previous findings, a study of the pharmacokinetics of antituberculous drugs in HIV-infected patients found that rifampin kinetics were widely variable and often resulted in subtherapeutic serum concentrations. INH concentrations were subtherapeutic in one-third of patients, while PZA kinetics were acceptable. (*IDSA #624.*)

Hepatitis. Twenty-two HIV-infected patients with HCV coinfection were treated with interferon alpha with or without ribavirin. After 12 weeks of therapy, the early virologic response rate was eight of 16 (50%) in the combination therapy group and only one of 11 (9%) among those treated with interferon alpha. There was no change from baseline in plasma HIV RNA (including in those receiving antiretroviral therapy with AZT or d4T, drugs potentially antagonized by ribavirin). The median

CD4 T cell change was - 24 cell/mm^3. (*IDSA #692.*)

Ten (5 genotype 3, 5 genotype 1) of 20 HCV coinfected patients had undetectable plasma HCV RNA after six months of treatment with interferon alpha and ribavirin. (*ICAAC #104.*) The treatment-related anemia commonly seen with this regimen was successfully managed by administration of erythropoietin. (*ICAAC #105.*)

HAART administration to HCV coinfected patients had no effect on HCV viral load but, in those who achieved and maintained undetectable plasma HIV RNA, there was a significant increase in serum transaminases not observed in those with incomplete HIV suppression. This enzyme increase correlated with the rise in CD8 cell count and may have represented the effects of an enhanced immune response. (*ICAAC #102.*)

A similar effect was seen in hepatitis B virus coinfection. Two patients had exacerbations of chronic hepatitis B virus infection, manifested by rises in aminotransferase levels and HBV DNA, coincident with a virological and immunological response to HAART. Although one was receiving lamivudine, his HBV was resistant to this drug. (*IDSA #241.*) Seventeen HBV coinfected patients were treated with lamivudine, indinavir, and either zidovudine or stavudine for 24 months. For the duration of therapy, 82% maintained suppression of plasma HBV DNA. (*ICAAC #2057.*)

A retrospective analysis found 35 HIV-infected patients who developed acute hepatitis A virus infection. This resulted in interruption of HAART for a mean of 57 days, with 11% requiring hospitalizaiton, but no deaths. A case-control study found that, at one year, the viral load was significantly higher in cases than in controls and that only 16% of cases had a plasma viral load less than 400 copies/mL compared to 40% of controls (P = 0.03). (*ICAAC #97.*) This provides additional data indicating that vaccination against hepatitis A virus infection is warranted in HIV-infected patients.

The major risk factors for the development of hepatic toxicity after initiation of HAART were coinfection with HCV and/or HBV. (*ICAAC #113.*) Hydroxyurea administration did not cause hepatotoxicity in 12 patients with HCV coinfection. (*ICAAC #100.*)

Anemia. Once weekly dosing of erythropoietin (40,000 U with titration to 60,000 U if necessary) provides results at least as good as that of historical results from thrice weekly dosing in HIV infected patients with anemia. (*IDSA #528; ICAAC #1313.*)

Gastrointestinal Infections. Retrospective analysis of a large cohort of patients found no evidence that the use of macrolide prophylaxis for MAC was protective against the development of cryptospopridiosis. (*IDSA #400.*)

HIV Vaccines

Vaccination with a variety of HIV-1 antigens delivered in a canarypox vector was associated with the development of CD8+ CTL cells in 30%; these persisted for up to two years in 23-27%. (*IDSA #378.*)

An oligomeric HIV-1 gp160 MN/LAI-2 vaccine was administered to HIV seronegative adults in a Phase I trial. Neutralizing antibody to HIV-1MN, but not to HIV-1IIIB, was elicited in 17 of 19 recipients. Although in vitro mononuclear cell proliferation in response to gp160 was elicited, no CTL activity was detected. (*IDSA #381.*)

The administration of a DNA plasmid vaccine containing HIV-1 genes encoding rev and env was safe and elicited lymphocyte stimulation and cytotoxic T-cell responses to cognate antigens in recipients. (*IDSA #651.*) ❖

New Tricks for an Old Enterovirus

ABSTRACTS & COMMENTARY

Synopsis: *An outbreak of enterovirus 71 in Taiwan in 1998 resulted in more than 1 million cases of hand-foot-and-mouth disease or herpangina. Severe disease, especially rhombencephalitis, and fatalities from pulmonary edema and hemorrhage were observed, especially in young children.*

Sources: Ho M, et al. An epidemic of enterovirus 71 infection in Taiwan. *N Engl J Med* 1999;341:929-935; Huang CC, et al. Neurologic complications in children with enterovirus 71 infection. *N Engl J Med* 1999;341:936-942.

In 1998, an epidemic in taiwan of enteroviruses caused 129,106 cases of hand-foot-and-mouth disease or herpangina, which was estimated to represent less than 10% of the total number of cases. There were 405 cases of severe disease: aseptic meningitis, encephalitis, acute flaccid paralysis, pulmonary edema or hemorrhage, and myocarditis. There were 78 deaths, including 71 (91%) in children younger than 5 years of age, primarily resulting from pulmonary edema or hemorrhage. Enterovirus was isolated from 49% of outpatients with

uncompleted hand-foot-and-mouth disease or herpangina, 75% of hospitalized patients who survived, and 92% of patients who died.

During the 1998 enterovirus epidemic in Taiwan, 41 children were hospitalized with culture-confirmed enterovirus infection and acute neurologic manifestations. The mean age of the patients was 2.5 years (range, 3 months to 8.2 years). Twenty-eight patients (68%) had hand-foot-and-mouth disease and six (15%) had herpangina. Three neurologic syndromes were observed: aseptic meningitis in three patients, rhombencephalitis (brain-stem encephalitis) in 37 patients, and acute flaccid paralysis in four patients, which followed rhombencephalitis in three patients. The most common symptoms were myoclonic jerks, and T2-weighted magnetic resonance imaging (MRI) showed high-intensity lesions in the brain stem in 17 of 24 (71%) patients. Five patients with rhombencephalitis died.

COMMENT BY HAL B. JENSON, MD, FAAP

Since enterovirus 71 was isolated in 1969, it has been recognized to cause sporadic cases and several large outbreaks in many parts of the world. Enteroviruses, as their name implies, are spread primarily by the fecal-oral route but the characteristics of this outbreak indicate potential respiratory spread.

The unusual complications of rhombencephalitis suggest that this enterovirus could represent a particularly virulent strain, with tropism for the rhombencephalon. Rhombencephalitis was manifest by: myoclonic jerks with tremor, ataxia, or both (Grade I); myoclonus with cranial nerve involvement, including ocular disturbances such as nystagmus, strabismus, or gaze paresis (Grade II); or transient myoclonus rapidly followed by loss of doll's eye reflex, and apnea (Grade III). This outbreak was also characterized by pulmonary edema and hemorrhage, another uncommon although recognized complication of enterovirus 71 infection, which was responsible for the majority of deaths.

We tend to consider enterovirus encephalitis as sporadic, self-limited, and, generally, without serious morbidity and with low mortality. This outbreak showed the epidemic and fatal aspects of enterovirus 71 infections. Patients with neurologic symptoms following hand-foot-and-mouth syndrome or herpangina, or with encephalitis of uncertain etiology, should be cultured for enterovirus infections. This may hasten the diagnosis in sentinel patients and lead to earlier recognition of enteroviral outbreaks complicated by neurologic involvement. (*Dr. Jenson is Chief, Pediatric Infectious Diseases, University of Texas Health Science Center, San Antonio, TX.*) ❖

Long-Term Course of Hepatitis C Viral Infections in Children

ABSTRACTS & COMMENTARY

Synopsis: *Fourteen percent of German children who had undergone cardiac surgery before implementation of donor screening of blood donors were positive for antibodies against hepatitis C virus (HCV) and 55% of these antibody-positive children had circulating HCV. Liver function tests and liver biopsy of these children showed a small number of patients with significant liver disease. Children with hemophilia exhibited a high circulating HCV load but had less severe liver histopathology compared to children who had acquired HCV either from blood transfusions or vertically.*

Sources: Vogt M, et al. Prevalence and clinical outcome of hepatitis C infection in children who underwent cardiac surgery before the implementation of blood-donor screening. *N Engl J Med* 1999;341:866-870; Zellos A, et al. High viral load and mild liver injury in children with hemophilia compared with other children with chronic hepatitis C virus infection. *J Pediatr Gastroenterol Nutr* 1999;29:418-423.

German children who underwent cardiac surgery before 1991, when routine blood donor screening for hepatitis C was introduced, were studied for hepatitis C virus (HCV). Sixty-seven of 458 patients (14.6%) had antibodies against HCV. The positive rate in normal age-matched controls was only 0.7%. At a mean follow-up time of 19.8 years, 37 of 67 antibody-positive patients (55%) had detectable HCV RNA in their blood. Only one of the HCV RNA-positive patients had elevated alanine aminotransferase (ALT). Seventeen of 37 patients had liver biopsy. Three of these had histologic signs of progressive liver damage, and these three patients had additional risk factors.

Zellos and associates evaluated whether the mode of transmission of HCV infection had an effect on subsequent liver injury and circulating viral load of children with HCV infections.

Thirty-nine children who had positive enzyme-linked immunoassay (ELISA) immune tests for HCV antibodies were divided into three groups reflecting their route of infection: blood transfusions, hemophilia factor replacement therapy, and vertical transmission from mother to infant. Serum HCV viral load was approximately five times higher in the hemophiliacs than in the

other groups. Surprisingly, however, the degree of histologic liver injury (including inflammation and fibrosis) was significantly less severe in the hemophiliac boys compared to the other groups.

Group 1 consisted of nine children, 13.3 ± 0.9 years of age, who had a history of whole blood or red blood cell (RBC) transfusions. Group 2 consisted of 19 hemophiliac boys, 11.6 ± 0.8 years of age. Group 3 consisted of 10 children, aged 4.7 ± 1.1 years old, who presumably had vertically acquired HCV resulting from maternal to neonate transmission. Liver function tests (serum ALT), HCV viral load determined by polymerase chain reaction assay that measures the number of circulating viral copies per mL of blood, HCV genotype, and liver histology were assessed in all of these children and the results in the three groups were compared.

Despite a considerably shortened duration of infection, the children in group 3 with vertically acquired HCV infections had liver injury comparable to those in group 1. Genotype of the HCV infection did not influence either the level of viremia or histologic liver injury. Vogt and colleagues and Zellos et al conclude that children with hemophilia had higher levels of circulating HCV, but paradoxically had less evidence of hepatic damage than children who had acquired HCV by blood transfusions or vertical transmission at birth. Host resistance factors may have an important influence in the pathogenesis and expression of this disease.

COMMENT BY HOWARD A. PEARSON, MD, FAAP

There are few data on the prevalence and clinical outcome of HCV infections in children. These two papers examine this issue from somewhat different perspectives. In adults who have chronic HCV infections, the severity of subsequent hepatocellular disease may be influenced by the mode of transmission of the virus to the patient. This has not been studied in children. The report of Zellos et al showing a marked difference in the prevalence of persistent viremia in hemophiliac boys who were infected by virus contaminated Factor VIII but less severe hepatocellular damage compared to infections resulting from blood transfusions or vertical transmission suggest the possibility that host immune responses may affect the clinical expression of this disease. The finding of such a large group of HCV-infected hemophiliac boys is distressing, following as it does the 1980-1985 infection of about 70% of these boys with HIV that has virtually wiped out a generation of them. The present replacement therapies for hemophilia A are increasingly produced *in vitro* by recombinant DNA technologies and should be free of virus.

Vogt et al show that although there was a substantial risk of acquiring HCV infection from nonscreened blood transfusions, after about 20 years the virus had spontaneously cleared in many patients, and the clinical course in those still infected appeared more benign than would be expected in persons infected in adult life.

Even today, when extensive testing of blood has essentially eliminated most of the diseases that are now known to be transmissible, such as HIV and hepatitis A, B, and C, there could well be currently unknown viruses that are lurking or could enter the blood supply in the future. Only when these viruses and the diseases that they produce are recognized and appropriate testing is developed to detect them, there is at least a theoretical risk of repetition of the hepatitis C and HIV disasters of the last 25 years. As a hematologist, I would be the last person to argue against the appropriate use of blood products. However, transfusion of blood products has at least a theoretical risk of transmitting serious and even fatal diseases and they should not be administered for trivial or unnecessary indications. (*Dr. Pearson is Professor of Pediatrics, Yale University School of Medicine.*) ❖

CME Questions

48. True statements concerning enterovirus 71 include all of the following *except*:

a. it is an etiologic agent in some cases of herpangina and hand-foot-and-mouth disease.
b. severe complications occur more in young children than in adults.
c. it may produce lesions in the brain stem demonstrated by MRI.
d. they are exclusively spread by the fecal-oral route.

49. True statements about hepatitis C viral infections in children who had undergone cardiac surgery in infancy before implementation of donor screening include all of the following *except*:

a. infections occurred in more than half of these children.
b. there was a high prevalence of detectable HCV in their blood one to three decades later.
c. infections caused severe, long-term hepatocellular disase.
d. the course was considerably less severe than observed in patients infected as adults.

In Future Issues:

ICAAC Infectious Diseases

UPDATES

By Carol A. Kemper, MD, FACP

Renal Complication of IVIg

Source: Letter from the FDA, September 29, 1999.

The fda has alerted physicians to the risk of acute renal failure associated with the administration of intravenously administered immune globulin (IVIg). A total of 114 cases of renal dysfunction and acute renal failure have been reported in association with infusion of IVIg; although most patients recovered with supportive care, 17 cases were fatal. Most of the patients were older or had severe underlying disease. Just over half the cases occurred in patients with ITP, who often receive multiple sequential infusions at higher dosages compared with other recipients.

Histopathology available in 15 cases demonstrated acute tubular necrosis, vacuolar degeneration, and osmotic nephrosis—suggestive of osmotic injury to the proximal tubules. Indeed, 88% of U.S. cases of renal toxicity occurred in patients receiving sucrose-containing products, which are hyperosmolar. Available sucrose-containing products include those manufactured by the Central Laboratory, Swiss Red Cross (distributed by Novaritis Pharmaceuticals as Sandoglobulin® and the American Red Cross as Panglobulin®), which are responsible for 69% of reported cases, and Gammar® products, which are responsible for another 22% of reported cases. An additional 9% of cases have been associated with nonsucrose-containing products.

The FDA stressed that caution should be used when administering these products to patients who are elderly, have diabetes, pre-existing renal disease, paraproteinemia, evidence of volume depletion, or hypotension. Patients should be adequately hydrated before receiving these products. While the duration of infusion time has not been analyzed as a factor, these products should be administered as slowly as is practical (no more than 3 mg sucrose/kg/min or approximately 2 mg/kg/min for Sandoglobulin® and Panglobulin® and 1 mg/kg/min for Gammar® -P.I.V. products). You might want to check with your pharmacist for assistance when calculating the timing of an infusion. Patients should be advised of the potential risk of kidney damage and instructed to report any symptoms associated with fluid overload or decreased urine output. ■

Chronic Leg Ulcers Due to Hydroxyurea

Source: Sirieix ME, et al. *Arch Derm* 1999;135:818-820.

Hydroxyurea (hu) has been widely used in the suppression of chronic myeloproliferative disorders, as well as, more recently, in the treatment of HIV. A lesser known side effect of this agent is the development of chronic lower extremity ulcerations, which occurs in up to 8.5% of patients with myeloproliferative disorders receiving continuous HU therapy.

Sirieix and colleagues reviewed a total of 41 cases of chronic lower extremity ulcerations in patients receiving chronic maintenance therapy with HU for hematologic malignancy (mean duration of therapy, 5 years). Most of the patients were elderly and had poor wound healing, although there was no evidence of vascular compromise. The ulcerations promptly resolved in 80% of patients when HU was withheld. While the cause is not known, it has been suggested that the ulcerations may be the result of stasis changes from megaloblastic red cells, similar to that seen in hereditary blood dyscrasias, such as thalasemia, sickle cell disease, and spherocytosis. Interestingly, similar lower extremity ulcerations have not been described in patients with HIV infection, although macroerythrocytosis commonly occurs in those receiving zidovudine and HU. Topical GM-CSF has also been described as of potential benefit in the promotion of wound healing in some cases. ■

Moxifloxacin Penetrates Inflamed Skin

Source: Muller M, et al. *Antimicrob Agents Chemother* 1999;43:2345-2349.

Moxifloxacin is a promising new quinolone antibiotic with activity similar to trovafloxacin. To investigate the concentration of drug achieved in different body compartments in people, 12 healthy volunteers received a single oral dose of 400 mg or a single intravenous bolus of 400 mg over one hour. Concentrations of drug were measured in cantharides-induced skin blisters, saliva, and capillary plasma. Concentrations of free unbound drug in plasma rapidly equilibrated with the interstitial compartment. While the levels of moxifloxacin in capillary plasma and saliva were similar to that in plasma, the concentration of drug in skin blisters was 50% greater. These data suggest that moxifloxacin has excellent penetration of inflammatory interstitial fluid and damaged soft tissues. ■