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## INSIDE

*When mononucleosis does not get better* **page 88**

*Tenofovir-associated nephrotoxicity* **page 89**

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*Infectious Disease Alert's* Physician Editor, Stan Deresinski, MD, FACP, serves on the speaker's bureau of Merck, Pharmacia, GlaxoSmithKline, Pfizer, Bayer, and Wyeth, and does research for Merck. The Peer Reviewer, Connie Price, MD, reports no consultant, stockholder, speaker's bureau, research, or other financial relationship with any company related to this field of study. Updates author Carol A. Kemper, MD, FACP, does research for Abbott Laboratories and GlaxoSmithKline, and is on the speaker's bureau for Pfizer and Sanofi-Aventis.

# Mitochondrial Toxicity Associated with Linezolid

ABSTRACTS AND COMMENTARY

***By Dean L. Winslow, MD, FACP***

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***Synopsis:*** *Six patients developed lactic acidosis during prolonged linezolid therapy, possibly as the result of mitochondrial protein synthesis.*

**Sources:** Palenzuela L, et al. Does Linezolid Cause Lactic Acidosis by Inhibiting Mitochondrial Protein Synthesis? *Clin Infect Dis*. 2005;40: e113-e116; Soriano A, et al. Mitochondrial Toxicity Associated with Linezolid. *N Engl J Med*. 2005;353:2305-2306.

LINEZOLID IS AN OXAZOLIDINONE ANTIBIOTIC WHICH HAS proven to be very useful in the treatment of Gram positive bacterial infections, including methicillin-resistant *S. aureus* (MRSA). Its lipophilic properties and good penetration into pulmonary tissue allow it excellent activity in vivo in pneumonia due to MRSA, and its superiority to vancomycin has been demonstrated in clinical trials. While generally well-tolerated when given short term with prolonged therapy, myelosuppression (especially thrombocytopenia) is commonly seen. Less commonly, peripheral neuropathy and metabolic acidosis have been seen in linezolid treated patients.

Palenzuela and colleagues describe 3 patients who developed lactic acidosis while receiving prolonged linezolid therapy. Peripheral blood samples from these patients were examined by sequencing PCR fragments amplified from 12S and 16S rRNA, and direct sequencing of the PCR products was performed to identify known polymorphisms. To determine the frequency of polymorphisms in 100 control patients, restriction fragment length polymorphism (RFLP) analysis was performed using

restriction enzymes to specifically identify the substitutions in question. One patient was found to have a homoplasmic A2706G in 16S rRNA, one patient had a homoplasmic G3010A in 16S rRNA, and the third patient had no rRNA polymorphisms identified.

Soriano and colleagues also describe 3 patients who experienced linezolid-induced mitochondrial toxicity manifested by weakness and lactic academia. In all patients, mitochondrial respiratory chain complex II (succinate dehydrogenase, synthesized by cytoplasmic ribosomes) demonstrated normal activity in PBMC samples, but complex IV (cytochrome c oxidase, synthesized by mitochondrial ribosomes) activity was reduced.

## COMMENTARY

Linezolid inhibits bacterial protein synthesis by binding to the 50S ribosomal subunit and prevents the formation of the initiation complex which requires interactions with tRNA, mRNA, and the 30S ribosomal subunit.[1,2] Due to the similarities between the conserved domains of rRNAs in bacterial and human mitochondrial ribosomes, it is likely that linezolid causes mitochondrial toxicity by inhibiting protein synthesis. The 16s rRNA polymorphisms described by Palenzuela et al in 2 patients may confer genetic susceptibility to linezolid toxicity in a manner similar to the A1555G substitution in mitochondrial 12S rRNA, which confers susceptibility to aminoglycoside-induced hearing loss.[3] While chloramphenicol is seldom used now, older physicians were quite familiar with manifestations of mitochondrial toxicity associated with the use of this agent, which included anemia (which occurred commonly in patients treated for more than a few days) and the rarely seen grey baby syndrome of cardiovascular collapse in premature neonates associated with reduced metabolism of the drug. Chloramphenicol exhibits reversible binding to the 50S subunit of the bacterial ribosome at a locus which prevents the attachment of the amino acid-containing end of the aminoacyl-transfer RNA to its binding region.[4] Another class of antimicrobial agents commonly recognized as causing mitochondrial toxicities includes the nucleoside analogue HIV reverse transcriptase inhibitors, particularly the dideoxynucleoside agents. Nucleoside analogue toxicity is most commonly manifested by peripheral neuropathy, lipoatrophy, and less commonly by myopathy, encephalopathy, and hepatic steatosis with lactic acidosis.

Preclinical toxicity studies of linezolid performed by Pharmacia/Upjohn in rats and dogs, in retrospect, suggests mitochondrial toxicity, although specific studies to show this was the mechanism of toxicities observed were not performed. Myelosuppression was observed in both rats and dogs, which was time- and dose-dependent.[5] In addition, decreased food consumption, diarrhea, and mucosal histopathological changes (atrophy of intestinal mucosa and necrosis of crypt epithelial cells) were observed in rats. While not seen in the Pharmacia/Upjohn preclinical studies, the oxazolidinones were originally discovered by scientists at the DuPont Company, which advanced one compound, DuP 721, to Phase I clinical trials in the mid-1980s. Interestingly, the oxazolidinones were abandoned by DuPont in the late 1980s due to progressive fatal anorexia, which was seen in rats and dogs. My recollection is that nonspecific histopathologic changes similar to those reported by Pharmacia/Upjohn were seen in the DuPont preclinical pharm/tox studies. No mechanism of this was conclusively shown at that time but, in retrospect, it seems likely that this represented mitochondrial toxicity.

Due to its mechanism of action, it should not be surprising that linezolid is capable of causing mitochondrial toxicity. While linezolid is clearly an important drug for the treatment of antibiotic-resistant gram positive bacterial infections, clinicians should be aware of the potential for mitochondrial toxicity, particularly with prolonged therapy, and monitoring for myelosuppression and lactic acidosis should be routine. ■

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# When Mononucleosis Does Not Get Better

ABSTRACT & COMMENTARY

***By Joseph F. John, MD***

*Chief, Medical Subspecialty Services, Ralph H. Johnson Veterans Administration Medical Center, Professor of Medicine, Medical University of South Carolina, Charleston*

*Dr. John does research for Merck, is a consultant for Cubist, Roche, and bioMerieux, and is on the speaker's bureau for Pharmacia, GSK, Merck, Bayer, and Wyeth.*

***Synopsis:*** *The resolution of symptomatic IM is not determined by control of viremia, nor is it easily explained by altered host responses to EBV infection. The detailed determinants of delayed recovery remain to be elucidated.*

**Source:** Cameron B, et al. Prolonged Illness After Infectious Mononucleosis is Associated with Altered Immunity But Not with Increased Viral Load. *J Infect Dis*. 2006;193:664-671.

When primary Ebstein-Barr infection occurs in early childhood, it is usually asymptomatic. Infection later, during adolescence or in adulthood, is associated with a classic syndrome that we term infectious mononucleosis (IM), mono in the vernacular. There are patients whose mono does not resolve over a month or 6 weeks are considered to have chronic active Ebstein-Barr Virus infection (CAEBV). That type of prolonged illness—one in which fatigue and other symptoms persists more than 6 months—was the subject of an Australian study. The study evolved from a larger cohort being studied for acquisition of various infections over a long period time, known as the Dubbo Infection Outcome Study.

Participants in the Dubbo study were enrolled if their IgM antibody to EBV viral capsid antigen (VCA) was positive and if they had symptoms of IM. A health questionnaire known as SOMA-6 was used to follow the general symptoms of the cohort. A SOMA score of > 3 indicates severe disability. A control cohort was a group of IM patients who returned to health within 2 months. Assessments were performed on patients at 2-3 weeks, 4-6 weeks, and at 3 months. For those patients with symptoms > 3 months, further evaluation was performed, including detailed testing of EBV viral load, tests of humeral and cellular immunity, flow cytometry, and interferon-gamma determination (IFN-g). Controls were HLA matched.

The results were very interesting. Only 8 patients had prolonged illness. They were compared in the study to 31 controls. At the time of enrollment, the prolonged cases compared to controls had been in bed for a mean of 6 days and out of their normal roles for an average of 14 days. The mean time of illness for cases was 34 weeks compared to 8 weeks for controls. The mean time in bed for cases vs controls was 21 vs 5 days respectively.

IM is a disease that triggers a brisk cytotoxic lymphocytic response primarily with EBV-specific CD8+ cells, a humoral response to EBV nuclear antigens, and reduction of a measurable circulating viral load. For case patients as compared to controls, there was no abrogation of the CD8+ cell response, and the pattern of decline to normal was the same in both groups. The cases were more likely to show a blunted CTL response to latent antigens. Also, cases were more likely to have higher anti-EBNA at 3-6 weeks and at 3 months than the controls. Controls were more likely to develop quicker responses to specific lytic antigens. There was no significant difference in viral load between the 2 groups.

## COMMENTARY

This study helps resolve the issue of why some young adults (mean age of 23 years in this study)

resolve their primary EB virus infection very slowly. Common observation is that a youngster with mononucleosis gets better in about 2 months. Controls without prolonged illness health returned in about 8 weeks compared to 4 times as long in cases. Repeated psychological testing showed no differences between the 2 groups that would ascribe the chronic symptoms to alterations in mood.

IM also produces a peak gamma-interferon response in about 4-8 weeks, as measured for controls also in this study. Cases were more likely to take on the average of 30 weeks to reach a peak interferon response. In contrast, cases were more likely to make a slower antibody response to EBNA. Cameron and colleagues emphasize that this finding contradicts classic dogma (Henle, et al *Proc Natl Acad Sci*. USA 1987) that linked convalescence to a rising anti-EBNA, whereas that rising or persisting response to EBNA represents a delay in the humoral response.

EBV viral loads are now available at many tertiary care centers. It will be tempting to measure these levels in patients with unresolving IM. Nevertheless, this current study by Cameron et al found that their viral loads mitigated as early in cases as in controls, suggesting that it is not the virus per se that produces prolongation of the illness. It is more likely the differences in cytokine responses explain more of the differences in symptom recovery from IM.

It is interesting to me that many patients with chronic fatigue who may eventually be diagnosed as having chronic fatigue syndrome present at some point in their illness with elevated humoral responses to EBV. Studies have measured elevated interferon levels in patients with CFS. In Japan, CFS patients are referred to as having cytokine disease. The exact role of EBV in CFS remains elusive. At the very least with the development of numerous biologics that influence cytokine production, such agents may prove worthwhile to test in patients with prolonged EBV and possibly in patients with CFS. It is unlikely that chronic symptoms of lassitude, fatigue, and the need to remain in bed will be due to the effects of persisting whole virus. ■

# Tenofovir-Associated Nephrotoxicity

ABSTRACT AND COMMENTARY

***By Dean L. Winslow, MD, FACP***

***Synopsis:*** *Tenofovir disoproxil fumarate (TDF)-associated acute renal failure (ARF) was diagnosed in 5 HIV-infected patients and an additional 22 patients previously described in the literature are reviewed. ARF resolved in 22 of 27 patients after discontinuation of TDF.*

**Source:** Zimmermann AE, et al. Tenofovir-Associated Acute and Chronic Kidney Disease: A Case of Multiple Drug Interactions. *Clin Infect Dis*. 2006;42:283-290.

THIS PAPER REPORTS ON 5 HIV-INFECTED PATIENTS receiving TDF-containing antiretroviral (ARV) therapy who developed ARF. One patient had associated Fanconi syndrome/renal tubular acidosis (RTA). One patient who did not have RTA underwent renal biopsy, which revealed acute tubular injury with loss and irregularity of tubular epithelial cells. A literature review performed by Zimmerman and colleagues resulted in 22 additional cases of TDF-associated ARF. Looking at the combined cohort, the majority of patients recovered normal renal function following discontinuation of TDF, however GFR in 5 patients did not return to baseline values after a mean duration of follow-up of 7.5 months. Sixteen patients had RTA. Renal biopsies performed in 8 patients all revealed ATN with nuclear swelling and karyomegaly of proximal tubular nuclei. Development of nephrotoxicity did not appear to correlate with either CD4 count or HIV RNA level. However, nephrotoxicity was associated with concomitant treatment with RTV, LPV/r, ATV, or ddI.

## ■ COMMENTARY

The disastrous experience with nephrotoxicity associated with another Gilead Sciences nucleotide analog reverse transcriptase inhibitor, adefovir dipivoxil (ADV) dosed at either 120 mg or 60 mg daily, clearly sensitized clinicians to the potential for nephrotoxicity associated with this class of antiretroviral agents. Fortunately, despite widespread use of the related drug tenofovir disoproxil

fumarate (TDF), nephrotoxicity associated with TDF has fortunately been quite rare in both registrational trials and in clinical practice. In fact, in most of Gilead's Phase III registrational trials, the incidence of nephrotoxicity in the TDF arms has not significantly exceeded that seen in the control arms of these studies.

Despite the safety, potency, good tolerability, and convenience of TDF (also available in fixed combination with emtricitabine), most clinicians have now had patients in their practices develop TDF-associated renal failure. In contrast to the experience with ADV, where development of decreased GFR was usually preceded by development of RTA manifested by phosphaturia/hypophosphatemia, hyperchloremic metabolic acidosis, glycosuria, and low-level proteinuria, many cases of TDF-associated nephrotoxicity seem to present more acutely with an ATN-like picture.

This review makes a good case for the role of RTV (with or without LPV) as a contributing factor to the development of nephrotoxicity. Preclinical studies with both ADV and TDF consistently show a relative lack of mitochondrial toxicity with these agents as compared to the dideoxynucleoside analogue reverse transcriptase inhibitors (ddI and d4T). However, it is known that TDF is eliminated by active tubular secretion, as well as glomerular filtration. Nucleotides are actively taken up into the proximal renal tubular epithelial cells via hOAT1 located on the basolateral membrane of the proximal tubule.1 Once accumulated, nucleotides are secreted into the urine via multidrug-resistance protein 2 (MRP2), located on the apical side of the proximal tubule. Ritonavir is known to be a potent inhibitor of both MRP2 (as well as another efflux pump for organic cations, P glycoprotein), which provides a most plausible explanation for this toxicity in vivo.[2] My suspicion that the apparent weaker relationship with nephrotoxicity to atazanavir may be coincidental or possibly related to ritonavir boosting of ATV in some cases (the data on this are not clear in this paper) since ATV does not display significant inhibition of MRP2, although it is an inhibitor of P-glycoprotein, as well as CYP 3A.[3]

Tenofovir remains an important part of modern day antiretroviral therapy, but clinicians need to be vigilant for nephrotoxicity in TDF-treated patients, especially those who are receiving ritonavir-boosted protease inhibitor-containing regimens. ■


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# Linezolid for Gram-Positive Infections of Neutropenic Patients

ABSTRACT & COMMENTARY


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***Synopsis:*** *Linezolid given 600 mg q12 iv. to febrile neutropenic patients for suspected or proven infections due to Gram-positive bacteria with cancer showed similar efficacy and safety as vancomycin given 1 g q12h iv.*


**Source:** Jaksic B, et al. Efficacy and Safety of Linezolid Compared with Vancomycin in a Randomized, Double-Blind Study of Febrile Neutropenic Patients with Cancer. *Clin Infect Dis*. 2006;42:597-607.

THIS STUDY RAN FROM NOVEMBER 2000 TO MAY 2002, recruited 611 patients from 58 centers predominantly from Europe, and set out to compare the efficacy and safety of these drugs for treating febrile, neutropenic patients with cancer and either proven or suspected infection due to Gram-positive bacteria in a prospective, blinded randomized controlled trial. The primary end point was clinical success 7 days after completion of therapy and both drugs performed equivalently in the intent-to-treat analysis: 219 (87.3%) of 251 patients given linezolid compared with 202 (85.2%) of 237 patients given vancomycin. There was also no significance difference in results obtained for the modified ITT analysis, which examined the outcome of those with a proven

**Table 1**
**Infectious Complications at the Start of the Study**

| | n (%) |
|---|---|
| Number of patients in ITT population | 605 |
| Fever of uncertain origin | 183 (30) |
| Bacteraemia of unknown source | 180 (30) |
| Vascular catheter related infection | 65 (11) |
| Pneumonia | 50 (8) |
| Skin and soft tissue infection | 47 (8) |
| Urinary tract infection | 5 (1) |
| Other | 75 (12) |

infection due to a Gram-positive bacterium: 55 [87.3%] of 63 patients given linezolid compared with 43 [86%] of 50 patients given vancomycin.

There were also 2 other analysis done with results that were equivalent for the 2 drugs: clinically evaluable analysis (ie, patients who had received at least 80% of intended therapy for at least 3 days to determine failure and 7 days to determine success); 171 [92.4%] of 185 patients given linezolid compared with 158 [89.3%] of 177 patients given vancomycin and microbiologically evaluable analysis (ie, episodes that involved a gram positive bacterium that was susceptible to the study drug); 41 [87.2%] of 47 patients given linezolid compared with 32 [86.5%] of 37 patients given vancomycin.

The mean time to defervescence was shorter for linezolid than for vancomycin in the modified ITT (6.6 vs 8.5 days) and microbiologically evaluable episodes (5.9 vs 9.1 days). Mortality rates in the ITT subset were 17 [5.6%] of 304 patients vs 23 [7.6%] of 301 patients, though linezolid was associated with fewer drug-related adverse events (52 [17.2%] of 303 patients vs 72 [24.0%] of 300 patients) and fewer cases of drug-related renal failure (1 [0.3%] of 303 patients vs 7 [2.3%] of patients). Hence, it was concluded that treatment with linezolid and vancomycin resulted in similar efficacy and safety outcomes for febrile neutropenic patients with cancer.

## COMMENTARY

At almost every level there was little to choose between linezolid and vancomycin as therapy for proven or suspected Gram-positive bacterial infections in febrile neutropenic patients. There weren't even any major differences in drug reactions. However, patients needed 2 days less linezolid than vancomycin to achieve the same result. So far so good. So, should we all move over to linezolid for this indication? The answer is actually a resounding No, not because of the drug but rather because it is no longer considered prudent to modify initial empirical therapy empirically by adding a drug that provides better cover against Gram-positive bacteria. In fact, the goals posts on this playing field had already begun moving between completion of the study and this publication. This is not meant as a criticism of this study, which actually nicely reflects the practice of may institutions at that time. This can be seen by the fact that only 15% of all episodes were evaluable for microbiological assessment, that almost 30% of patients were entered solely on the basis of fever of unknown origin, and by the rather high use of additional drugs particularly antifungal agents starting after the first day of the protocol presumably also for empirical therapy.

While the study was being wrapped up, the IDSA published a new set of guidelines that recommended that empirical vancomycin therapy should only be considered for high-risk patients, namely those with clinically suspected serious catheter-related infections (eg, bacteremia, cellulitis, those known to be colonized with penicillin- and cephalosporin-resistant pneumococci, or methicillin-resistant *Staphylococcus aureus*), those with bacteremia due to Gram-positive bacteria pending identification and susceptibility test results, and those with hypotension or other evidence of cardiovascular impairment.[1] A later study concluded that empirical vancomycin offered no measurable benefit to persistently febrile and neutropenic patients with cancer unless there was evidence of lung infiltrates, septic shock, clinically-defined infections likely to be due to Gram-positive bacteria, such as catheter-related or skin- and soft-tissue infections or gram-positive bacterial infections due to bacteria shown to be resistant to the initial empirical regimen.[2] So on this basis, therapy with linezolid or vancomycin would still have been justified for up to 70% of patients entered into the current study.

What then would help the clinician decide to favor one drug over the other? This is tricky because on the one hand linezolid was more effective in eradicating enterococci than was vancomycin, and a saving of about 2 days treatment might be made. On the other hand though, both drugs are well tolerated; a shadow still hangs over linezolid in terms of its potential to prolong neutropenia and thrombocytopenia, though there was little evidence of either in the current. Perhaps the ability to switch from parenteral to oral linezolid might, in the end, cut the mustard, since patient could be discharged earlier.

Whatever the verdict, it is worth noting that it has actually taken over 20 years to settle the place

of empirical therapy for gram-positive bacterial infections in febrile neutropenia patients. Now, there is also a choice that not only includes vancomycin and linezolid but also teicoplanin, at least in Europe and perhaps daptomycin.[3,4] Given the relatively indolent nature of many of the gram-positive bacterial infections, particularly those involving the coagulase-negative staphylococci, the availability of useful guidelines and the pressing need for prudent antimicrobial use let us hope that these drugs will be employed more on the basis of evidence and less empirically than has been the case hitherto. ■

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# Tropical and Geographic Medicine

SPECIAL FEATURE

***By Stan Deresinski, MD, FACP***

*The following is a summary of selected abstracts of papers presented at the 54th Annual Meeting of the American Society of Tropical Medicine and Hygiene which took place from December 11-December 15, 2005 in Washington, DC.*

## Refugees

THIRTY-THREE OF THE MORE THAN 3000 "LOST boys of Sudan" (mean age, 25 years) in the United States were evaluated. All but 6 reported chronic abdominal pain. Ten (48%) of 21 had *Schistosoma mansoni* and one had *S. haematobium* infection, while 5 (20%) of 25 were HBsAg carriers and 3 (12%) of 25 had chronic hepatitis due to HBV. Three were found to have *Entamoeba histolytica* infection. Cases of filariasis and strongyloidiasis were identified, as were several cases of *Helicobacter pylori* infection. Most were lactose intolerant.

Since 1999, the CDC has recommended that all refugees from Southeast Asia and Africa receive a single oral dose of 600 mg albendazole prior to embarkation for the United States. Strongyloides was highly prevalent in Southeast Asians while Schistosoma was frequently found in Africans. Since the introduction of this policy of empiric presumptive therapy, the prevalence of individuals in whom there was detection of at least one stool helminth decreased from 21.5% to 8.4%. There were significant reductions in the frequency with infestation due to Trichuris, Ascaris, hookworm, or Strongyloides. Thus, empiric single-dose albendazole is effective in reducing the prevalence of intestinal parasitic infection in refugees, but does not eliminate the problem.

## Nematode Infections

### Onchocerciasis

Several studies demonstrated the benefit of annual mass drug administration, with ivermectin for control of onchocerciasis.

### Lymphatic Filariasis

Antibiotic therapy directed at Wolbachia, the Gram-negative bacillary endosymbiont critical to reproduction of *Wucheria bancrofti*, is associated with reduced microfilaremia. The plasma concentration of vascular endothelial growth factor (VEGF), which is important in the growth and differentiation of vascular and lymphatic endothelial cells and which is also associated with increased vessel permeability, are increased in patients with lymphatic filariasis. In a placebo-controlled, randomized trial in Ghana, a 6-week course of doxycycline following single initial doses of ivermectin and albendazole (the control group received an ivermectin placebo plus albendazole) was associated with significant reductions in microfilaremia and Wolbachia bacterial loads per microfilaria. Also reduced were mean supratesticular lymphatic vessel dilatation and the frequency of detection of the filarial dance sign, an indicator of macrofilaricidal activity. Mean plasma VEGF-C concentration was reduced, as was that of its soluble receptor, sVEGFR-3. Thus, doxycycline therapy aimed at eliminating Wolbachia reverses some of the pathophysiological factors operative in lymphatic filariasis.

In a randomized trial, single-dose treatment with diethylcarbamazine alone appeared to be as effective as its combination with albendazole in the treatment of bancroftian filariasis in Papua New Guinea.

In several villages in Papua New Guinea, 2 annual administrations of albendazole and diethyl carbamazine were associated with a decrease in the prevalence of microfilaremia from 20.5% to 3.5% and a significant decrease in the prevalence of mosquito infection. Annual mass drug administration was also associated with significant decrease in the incidence of acute adenolymphangitis in Papua New Guinea.

### Visceral Larva Migrans

A 16-year-old girl ate an earthworm on a dare. One month later she developed cough, multiple pulmonary nodules due to eosinophilic organizing pneumonitis, and an eosinophil count of 32,000/mm$^3$. Testing of serum found an antibody titer of > 1:4096 to Toxocara. The earthworm apparently served as a carrier of larvae of Toxocara from soil to patient. This case has been published (Cianferoni A, et al. *Pediatrics*. 2006;117:e336-e339).

## Trematode Infections

### Schistosomiasis

All 120 patients with a diagnosis of schistosomiasis in Israel from 1994-2003 had traveled to sub-Saharan Africa. Of the total, 65% swam in Lake Malawi and 23% had rafted on the Omo River in Ethiopia. Approximately one-third had *Schistosoma haematobium* infection, one-third were infected with *S. mansoni*, and the species was not determined in the remainder. Two-thirds of the 72 patients with detailed information had symptoms of acute schistosomiasis, with 52% having fever, 36% cough and shortness of breath, and 19% having urticaria. Thus, most cases present during early stage infection when ova may not be detectable in stool and when antiparasitic treatment with praziquantel has reduced efficacy.

## Cestode Infections

### Cysticercosis

In a study of 7 communities in northern Peru, identification of human cysticercosis hotspots within 50 meters of the residence of *Taenia solium* tapeworm carriers was made.

Investigators at the NIH have used methotrexate as a replacement of or supplement to corticosteroids as adjunctive anti-inflammatory therapy in neurocysticercosis patients with subarachnoid cysts, cysticercal meningitis, multiple ventricular cysts, inflammatory parenchymal cysticercosis, and refractory calcific cysticercosis associated with perilesional edema. All patients were reported to have dramatic improvement without serious side effects.

## Protozoan Infections

### Leishmaniasis

Of 57 patients with mucocutaneous leishmaniasis due to *L. braziliensis* in Bolivia who completed 6 months of follow-up after treatment with miltefosine, 54 (85%) had improved while the remainder were unchanged.

In a double-blind, placebo-controlled trial, 23 patients in Brazil with mucosal leishmaniasis were given stilbamidine for 30 days with randomization to also receive either pentoxifylline 400 mg tid or placebo for 30 days. All pentoxifylline recipients, but only 42% ($P = 0.037$) of placebo recipients, were cured. The mean time to lesion healing was significantly shorter in the pentoxifylline arm (84 days vs 146 days). No relapses were observed in either arm after one year.

### Malaria

Three hundred ninety eight-children in Papua New Guinea with severe malaria by the WHO definition (asexual parasitemia plus recent seizures or coma or respiratory distress or hemoglobin < 5 g/dL) were evaluated. Of those with mixed plasmodial infection, 15.7% had severe malaria, as did 11% with *P. falciparum infection*, 14.5% with *P. vivax*, and 6.4% with *P. malariae*. Seizures occurred in 22% of *P. falciparum* and 26% of *P. vivax* infections, while 2% and 3%, respectively, experienced coma. Respiratory distress occurred more frequently in those with *P. vivax* (58%) than in *P. falciparum* infection (40%). This report flies in the face of the common perception that *P. vivax* infection is almost invariably mild-to-moderate in severity and seldom life-threatening.

Of 102 evaluable nonimmune travelers with *P. falciparum* infection treated with artemether/lumefantrine, 95% had parasitological cure at 28 days. The mean time to parasitological clearance was 42 hours and that to fever resolution was 39 hours. Treatment was well tolerated.

Almost 500 patients in Mali with uncomplicated *P. falciparum* infection were randomized to treatment with either artesunate/mefloquine or artemether/lumefantrine. Although fever resolved more rapidly with the former regimen, there was no difference, after correction for reinfection (which occurred less frequently in the artesunate/mefloquine arm), in the 28 day cure rates (96% vs 97%). Vomiting occurred more frequently in those given artesunate/mefloquine (5.1%) than in recipients of artemether/lumefantrine (1.7%; $P = 0.042$).

Concern has been raised regarding the potential for the use of trimethoprim/sulfamethoxazole (TMP/SMX) as prophylaxis in AIDS patients in Africa to lead to resistance of *P. falciparum* to antimalarial agents targeting folic acid synthesis. In a prospective trial in an area of Kenya with a high preexisting level of malarial antifolate resistance, both HIV infected and non-HIV infected individuals were randomized to receive either TMP/SMX or a multivitamin daily for a mean of 5.4 months. While the number of multiple resistance mutations increased in both treatment arms, they did so with similar frequency. It was concluded that, at least in an area with a high frequency of preexisting antifolate resistance in *P. falciparum*, widespread use of TMP/SMX "is unlikely to contribute substantially to further increase in antifolate resistance."

One hundred adults in Thailand with uncomplicated *P. falciparum* infection were randomized to receive one of 4 regimens, 2 of which utilized azithromycin and artesunate and 2 azithromycin and quinine. The artesunate combinations arms had a significantly faster time to parasitological cure (33 hours vs 72 hours).

The frequent identification of *P. vivax* resistant to chloroquine and/or tolerant to primaquine has been increasing in Southeast Asia and the Southwest Pacific. Twenty-eight Vietnamese adults (mean weight, 49 kg) were treated with artesunate 200 mg bid for 2 days followed by primaquine 22.5 mg bid for 7 days. Blood stage parasites were eliminated within 24 hours in all patients, and no asexual parasites were detected during the 28 day follow-up period.

The failure rate of chloroquine treatment of *P. vivax* infection in Papua, Indonesia, is currently reported to exceed 70%. An open trial found that treatment with either artekin or amodiaquine had high degrees of efficacy.

HIV infection did not affect the response to therapy of uncomplicated malaria in Uganda.

## Bacterial Infections

### Salmonella Paratyphi

Of 64 individuals in the United States with *Salmonella paratyphi* A infections, almost all of those interviewed reported recent international travel, most to Southeast Asia. Twelve (75%) of 16 isolates tested were resistant to nalidixic acid, with most of the latter associated with travel to Southeast Asia. Treatment of infections due to nalidixic acid-resistant Salmonella with fluoroquinolones, such as ciprofloxacin, is known to have impaired efficacy, even though many of the isolates remain susceptible by current in vitro breakpoints.

## Viral Infections

### Nipah

Of 22 individuals in Bangladesh who had survived Nipah virus infection in 2003-2005, 17 (77%) had encephalitis and the remainder only a febrile syndrome. All but one reported disabling fatigue after recovery from the acute illness, with a mean duration of 2 months. One-third of those with prior encephalitis had persisting neurological dysfunction, but none had overt seizures.

### Dengue

A prospective evaluation of almost 3000 factory workers in Bandung, Indonesia, over 4 years identified 1431 febrile illnesses, of which 176 were due to dengue and 4 of the latter had 2 separate episodes of dengue. One individual with preexisting neutralizing antibody to DEN-1 developed DEN-3 infection followed by infection by an unknown serotype. Two subjects had preexisting antibody to DEN-2; one developed sequential infections with DEN-3 and DEN-1, while the other had subsequent DEN-4 and DEN-3 infections. One individual with preexisting antibody to DEN-2, 3, and 4 had subsequent infections due to DEN-4 (which manifested as dengue hemorrhagic fever) and DEN-3.

The lack of protection across serotypes is well known, but evidence of repeat infection with an organism of the same serotype, as seen in one individual, indicates lack of complete protection even within a serotype. In addition, despite these repeated infec-

tions, only one resulted in dengue hemorrhagic fever, a disease manifestation believed to be the result of immune enhancement in an individual with reinfection with a new serotype of the virus. ■

## CME Questions

8. **What is the likely explanation for persistence of symptoms in infectious mononucleosis due to Ebstein-Barr Virus?**
   a. Poor processing of viral capsid antigen by lymphocytes
   b. High viral loads
   c. Cytokine dysregulation
   d. Underlying psychological illness

9. **Which one of the following drugs is the most likely to be associated with the development of lactic acidosis?**
   a. Linezolid
   b. Tenofovir
   c. Vancomcyin
   d. Ritonavir

10. **Which of the following is correct?**
   a. Tenofovir is primarily metabolized by the liver.
   b. Empiric antibiotic therapy of febrile neutropenic patients must always include either linezolid or vancomycin.
   c. Previous infection with dengue virus type 1 protects against subsequent infection with all dengue types.
   d. *Plasmodium vivax* infection acquired in Southeast Asia or the Southwest Pacific is often recalcitrant to treatment with chloroquine.

**Answers:** 8. (c); 9. (a); 10. (d)

## CME Objectives

The objectives of Infectious Disease Alert are:

• To discuss diagnosis and treatment of infectious diseases;

• To present current data regarding use of new antibiotics for commonly diagnosed diseases and new uses for traditional drugs;

• To present the latest information regarding the pros, cons, and cost-effectiveness of new and traditional diagnostic tests;

• To discuss new information regarding how infectious diseases (eg, AIDS) are transmitted and how such information can lead to the development of new therapy. ■



## In Future Issues:

**Posaconazole**

# UPDATES

By Carol A. Kemper, MD, FACP

## California Influenza Strain Given the Boot

ProMED-mail March 3, 2006; promed@promedmail.org

THE CALIFORNIA INFLUENZA strain (A/California/07/2004 [H3N2]), first isolated in our own backyard in Santa Clara County, included in the 2005-2006 trivalent influenza vaccine, has been given the boot! Instead, the United States Advisory Committee on Immunization Practices has chosen a Wisconsin strain of Influenza A (A/Wisconsin/67/2005 [H3N2]) for next year's vaccine. Although many virus strains found circulating this year were related to A/California, there was an increasing prevalence of infections due to strains related to A/Wisconsin.

In addition, the Influenza B Shanghai strain is being replaced by a Malaysian strain of Influenza B (B/Malyasia/2506/2004), which is antigenically equivalent to an Ohio strain found in the United States. The third component of the vaccine will remain A/Caledonia/20/99 [H1N1]. Experts caution that the inclusion of 2 new strains of virus may create problems with vaccine production this year, as manufacturers have to create whole new batches of virus, with a bit less predictability in production. In the past 3 years, only one new strain of virus was introduced into vaccine production.

Global flu activity remains low this year, compared with recent years, with only scattered hot spots of greater flu activity in Europe. ■

## HBV, DNA, and Hepatocellular Carcinoma

Chen CJ, et al. Risk of Hepatocellular Carcinoma Across a Biological Gradient of Serum Hepatitis B Virus DNA Level. *JAMA*. 2006;295:65-73.

MORE THAN 350 MILLION PEOPLE in the world are infected with HBV, many of whom were perinatally infected or infected at a young age. These individuals are at significant risk for hepatitic cirrhosis, liver failure, and hepatocellular carcinoma. Earlier studies have confirmed that risk factors for developing hepatocellular carcinoma include male gender, older age, duration of infection, cigarette smoking, alcohol consumption, elevated transaminases, cirrhosis, and evidence of HBe antigen.

Now, Chen and colleagues have found a statistically significant relationship between higher levels of circulating HBV DNA and the development of hepatocellular carcinoma. Beginning in 1991, nearly 24,000 individuals in Taiwan agrees to participate in a prospective national cancer screening program. A total of 3563 individuals, aged 30-65 years, who were seropositive for Hepatitis Bs Ag and seronegative for HCV were included in this study. Of these, 15% were seropositive for HBe antigen, 6% had elevated serum ALT levels, and only 2% had cirrhosis at entry to study. About one-fourth had undetectable levels of plasma HBV DNA < 300 copies/mL, 32% less than 10,000 copies, and 17% had > 1 million copies.

During a mean follow-up of 11.4 years, there were 164 cases of hepatocellular carcinoma and 346 deaths. After adjusting for other risk factors, higher levels of HBV DNA were associated with a higher incidence of hepatocellular carcinoma, in a dose-response relationship. The cumulative incidence of hepatocellular carcinoma ranged from 1.3% in patients with undetectable levels of HBV DNA to 14.9% for those with > 1 million copies ($P < .001$). This relationship was strongest in those who were HBe Ag seronegative with normal liver function studies at entry to study.

Persistently high levels of circulating HBV DNA throughout the study were also associated with a greater risk of hepatocellular carcinoma. While fluctuations in HBV DNA occurred throughout the study, in part from intercurrent treatment, some patients spontaneously became HBe antigen seronegative. Follow-up serum samples collected a mean of 10 years later found that 42% of those who were initially HBe antigen seropositive were seronegative at the last sample available for testing. This group was less likely to have higher HBV viral loads > 100,000 than who remained positive for HBe Ag (55% vs 95%). Those with sustained high-level viremia and persistence of HBe Ag remained at the greatest risk for hepatocellular carcinoma. Nonetheless, even in those with loss of HBe antigen over time, sustained high-level viremia remained a strong predictor of hepatocellular carcinoma risk.

Based on the consistency of the dose-response relationship between HBV DNA levels and hepatocellular risk, Chen et al advocate for regular monitoring of HBV DNA levels, even in those patients previously perceived to be at lower risk (HBe Ag seronega-

tive, normal liver function studies and no evidence of cirrhosis). This data suggests the importance of close follow-up, routine radiographic screening and screening of alpha fetoprotein levels, and antiviral treatment, even in those patients who are HBe antigen seronegative with HBV DNA levels > 10,000. ■

## Disappearance of Rheumatic Fever in the United States?

Shulman ST, et al. Temporal Changes in Streptococcal M Protein Types and the Near-Disappearance of Acute Rheumatic Fever in the United States. *Clin Infect Dis*. 2006;42:441-447.

In the past year, I have seen 2 young Asian-Indian women, both in their late 20s and with small children, with acute rheumatic fever and polyarthritis. One gave a history of acute rheumatic fever (ARF) at age 11 in India, treated with prophylactic procaine penicillin injections for 5 years. One gave a history of an ARF-like illness at age 7 in India, never diagnosed as such at the time. Both had evidence of pre-existing rheumatic heart disease on echocardiogram. Both were evaluated by a number of different physicians for "fever of unknown origin" (one for about one month, and one for 4 days in hospital) before a diagnosis of ARF was made.

These 2 cases are probably the first and only cases of ARF I've seen in 18 years as an Infectious Disease physician. None of the other physicians involved in the care of these young women recalled ever having seen a case. It is interesting that both were essentially imported cases, although they had obviously been re-infected here in the United States.

Others have also observed the near-disappearance of ARF in the United States over the past ~30-40 years, postulating that better access to medical care, more rapid and effective diagnostic techniques and treatment of acute streptococcal pharyngitis, and less crowded living conditions may play a role. In addition, recent data suggests a diminished prevalence of M types of Group A streptococcus (GAS), which have higher toxin and M protein content, larger capsules (increased mucoidity), and are believed to be more rheumatogenic.

Shulman and colleagues examined the prevalence of rheumatogenic and non-rheumatogenic GAS types over the past ~40 years. While almost half (49.7%) of the 468 isolates collected from children with acute pharyngitis in 1961-1968 were rheumatogenic types, only 10.6% of 450 isolates obtained from children in Chicago and about 18% of 3969 isolates collected nationwide from 2000-2004 were rheumatogenic. During this interval, there was a virtual disappearance of enm strains, which encode for the M protein. At the same time, there was an increase in those strains believed to be non-rheumatogenic, which accounted for about 5% of cases of pharyngitis in earlier years, but about 28% of cases in 2000-2004.

Interestingly, the prevalence of M1 strains did not significantly change over time. This heterogeneous group of GAS are generally considered more likely to cause invasive disease, glomerulonephritis and acute renal failure, and toxic shock. This serotype was the most common M type found in Shulman's data in the 1960s and in the 2000s, and includes rheumatogenic strains. However, data suggests there may be genotypic shift occurring in these strains, with more of the current M1 strains producing an M protein different from classical, older rheumatogenic M1 strains.

This data is especially timely, with the recent completion of 2 Phase 1 trails of GAS vaccines. These 6-valent and 26-valent vaccines are based on M proteins, appear to be immunogenic and, unlike earlier attempts at vaccine development, do not appear to cross-react with human tissue proteins. About 90% of the recognized rheumatogenic types are included in the 26-valent vaccine, making it potentially an ideal candidate for clinical trails in developing countries endemic for ARF. However, vaccine development is still hampered by differing strain prevalences in different countries. ■

## Hepatitis A in Travelers

Mutsch M, et al. Hepatitis A Virus Infections in Travelers, 1988-2004. *Clin Infect Dis*. 2006;42:490-497.

Mutsch and colleagues tracked cases of Hepatitis A in Switzerland from 1988 to 2004, observing a significant reduction in cases of HAV infection over time, most likely from effective HAV vaccination of travelers. And yet, travel remains the biggest single risk for HAV infection. Recent travel accounted for nearly half (42%) of all HAV infections; 82% of these reported visiting friends or relatives. Risk factors for HAV infection with a travel history included younger age, foreign nationality, and exposure to a sick contact or contaminated food. The incidence of HAV infection in visitors to specific countries, in descending order, was Turkey, Kenya, India, Egypt, Brazil and Mexico. Mutsch and colleagues concluded that unvaccinated children of foreign born immigrants returning with their kids to visit friends and family in their country of birth are at the greatest risk for HAV infection. Special attention is required to reach these parents, who may perceive that the risk of travel to their home country is low, for pre-travel advice and appropriate vaccination of their non-immune children. ■

PHARMACOLOGY WATCH

Supplement to Clinical Cardiology Alert, Clinical Oncology Alert, Critical Care Alert, Infectious Disease Alert, Internal Medicine Alert, Neurology Alert, OB/GYN Clinical Alert, Primary Care Reports, Travel Medicine Advisor.

# Reversal of Atherosclerosis Via Intensive Statin Therapy

Aggressive LDL lowering with statins, so-called "very intensive statin therapy," leads to reversal of coronary atherosclerosis, according to a new study. The ASTEROID (A Study to Evaluate the Effect of Rosuvastatin on Intravascular Ultrasound-Derived Coronary Atheroma Burden) trial, a perspective, open label, blinded end-points trial, utilized the potent statin rosuvastatin in evaluating whether very intensive statin therapy resulting in LDL cholesterols in the low 60s associated with increases in HDL cholesterol could reverse atherosclerosis. Five hundred and seven patients were initially evaluated with intravascular ultrasound (IVUS) to determine baseline atheroma burden. Patients were then treated with intensive statin therapy with rosuvastatin 40 mg daily for 24 months, which resulted in an average LDL cholesterol of 60.8 mg/dL (mean reduction, 53.2%) and increased HDL cholesterol by 14.7%. IVUS was performed again at 24 months. The mean change in atheroma volume in the most diseased 10 mm sub segment was -6.1 (10.1) $mm^3$, with a median of -5.6 $mm^3$ ($P < .001$ vs baseline). Change in total atheroma volume showed a 6.8% median reduction. Adverse events were infrequent. Specifically there were no cases of rhabdomyolysis.

The authors conclude that lowering LDL-C to levels below currently accepted guidelines, when accompanied by significant increases HDL-C, can regress atherosclerosis in coronary disease patients, and is indicated for high-risk patients with established coronary disease (*JAMA*. 2006;295:1556-1565). An accompanying editorial notes that the study had several limitations, including lack of a control group or a comparator drug. They also note that the modest plaque reduction noted in this study "may not be the best measure of the treatment's effect on hard cardiovascular end points", however, they do applaud the pioneering work using intravascular ultrasound to help understand the anatomy and pathophysiology of coronary atherosclerosis and the effect of medical therapy on atheroma (*JAMA*. 2006;295:1583-1584).

### *Alternative Therapy for Depression?*

Patients who fail SSRI treatment for depression may respond to an alternative medication, or the addition of a second medication, according to 2 studies in the March 23 *New England Journal of Medicine*. In the first study, 727 adults with a nonpsychotic major depressive disorder who had no remission of symptoms or could not tolerate the SSRI citalopram (Celexa) were randomized to receive sustained release bupropion

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(Wellbutrin) in a maximal daily dose of 400 mg, sertraline (Zoloft) at a maximum daily dose of 200 mg, or extended release venlafaxine (Effexor-XR) at a maximal daily dose of 375 mg for up to 14 weeks. The primary outcome was remission of symptoms based on the Hamilton Rating Scale of Depression (HRSD-17). Secondary outcomes included scores on the Quick Inventory of Depressive Symptomatology (Self-Report) (QIDS-SR-16). Remission rates, as assessed by the 2 scales, respectively, were bupropion - 21.3% and 25.5%, sertraline - 17.6% and 26.6%, venlafaxine - 24.8% and 25.0%. Response rates based on the QIDS-SR-16 were bupropion 26.1%, sertraline 26.7%, and venlafaxine 28.2%. There was no significant difference with respect to outcomes, tolerability, or adverse effects among the 3 drugs.

The authors conclude that after unsuccessful treatment with an SSRI, 1 in 4 patients have a remission after switching to another antidepressant, and all 3 drugs in the trial were reasonable choices (*N Engl J Med*. 2006;354:1231-1242). Another option for treating patients who failed treatment with citalopram was explored in the second study in the same issue. In the study, 565 adults who had a nonpsychotic major depressive disorder without remission after 12 weeks of citalopram therapy were randomized to receive add-on therapy with sustained release bupropion up to 400 mg per day, and 286 were randomized to receive buspirone (Buspar) at a dose of up to 60 mg per day. The same depression rating scales were used in this study as in the previous study. For bupropion and buspiron, respectively, HRSD-17 remission rate was 29.7% vs 30.1%, QIDS-SR-16 remission rate was 30.9% vs 32.9%, and QIDS-SR-16 response rate was 31.8% vs 26.9%. Bupropion was associated with a greater change in QIDS-SR-16 score, as well as the overall lower QIDS-SR-16 score at the end of the study and a lower dropout rate to due to intolerance (12.5% vs 20.6%, $P < 0.009$).

The authors conclude that the addition of bupropion or buspirone to citalopram is useful; however, the addition of bupropion may have some advantages, including a greater reduction in the severity of symptoms in fewer side effects (*N Engl J Med*. 2006;354:1243-1252).

## FDA Actions

The FDA has approved the first generic HIV/AIDS drug for use in the United States. Zidovudine, manufactured under the trade name Retrovir by GlaxoSmithKline, was initially approved in 1987, and the company has had exclusive manufacturing rights until the drug's patent expired in September 2005. The generic is made by Aurobindo Pharma LTD of India. This is the same company that recently received approval from the FDA to co-package 3 antiretroviral drugs for the treatment of HIV/AIDS outside the United States. The regimen consists of lamivudine/zidovudine combination tablet along with efavirenz tablets. The co-packaging of these products has met the clinical safety, efficacy, and manufacturing quality standards required by the FDA. The approval is part of the Presidents Emergency Plan for offering full HIV treatment regimens for targeted areas of the world that are at risk to prevent HIV transmission and to treat AIDS and associated conditions. Patents and exclusivity prevent marketing of this combination in United States.

The FDA has approved a transdermal patch for the treatment of children with attention-deficit hyperactivity disorder. The patch delivers methylphenidate, the same ingredient found in Ritalin, in a daily patch that is applied early in the morning and removed 9 hours later. Methylphenidate patch is manufactured by Shire Pharmaceuticals and Noven Pharmaceuticals under the trade name Daytrana.

Salix pharmaceuticals has received approval to market a new tablet bowel prep for colon cleansing prior to colonoscopy. The virtually tasteless sodium phosphate tablets are an alternative to traditional liquid PEG bowel preps. The recommended dose is 32 tablets taken orally with a total of 2 quarts of clear liquids, administered as 4 tablets with 8 ounces of liquid every 15 minutes. Twenty tablets are given on the night prior to the procedure, with the remaining 12 tablets administered 3 to 5 hours prior to colonoscopy. Sodium phosphate tablets will be manufactured under the trade name OsmoPrep. ■