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An Alternate Effective Dosing Regimen for IV Artesunate

ABSTRACT AND COMMENTARY

By Lin H. Chen MD

Dr. Chen is Assistant Clinical Professor, Harvard Medical School and Director, Travel Medicine Center, Mt. Auburn Hospital, Cambridge, MA.

Dr. Chen has received research grants from the Centers for Disease Control and Prevention and Xcellerex

Synopsis: *A 3-dose regimen (12mg/kg total dose) of intravenous artesunate is comparable to the standard 5-dose regimen in achieving rapid parasite clearance and is very effective in treating severe malaria in African children.*

Source: Kremsner PG, et al. A simplified intravenous artesunate regimen for severe malaria. *J Infect Dis* 2012;205:312-9.

Currently, intravenous artesunate for the treatment of severe falciparum malaria is dosed at 0, 12, 24, 48, and 72 hours with a total dose of 12 mg/kg (5-dose regimen). Kremsner et al conducted a randomized, double-blind, placebo-controlled, dose-finding study in African children using a 3-dose regimen of IV artesunate at the same total dose. Patients were followed up clinically along with parasitological examinations weekly through day 28. This study utilized a product developed by the Walter Reed Army Institute of Research, and manufactured per current Good Manufacturing Practice (cGMP) guidelines by SRI International.

This study enrolled all African children from Gabon and Malawi, aged 6 months to 10 years, who had received a diagnosis of *Plasmodium falciparum* malaria with 5000 parasites/μL on initial blood smear, and whose severe illness required hospitalization. Among 197 children randomized, a total of 171 were in the "per protocol (PP)" population, with 86 in the 5-dose treatment group and 85 in the 3-dose treatment group; 156 continued through day 28 post treatment.

In the PP population, 78% of the 3-dose patients and 85% of the 5-dose patients achieved 99% parasite clearance in 24 hours, a -7.2% treatment difference. There were no significant differences in mean parasite reductions at either 24 or 48 hours.

Adverse events [AEs] were reported by 133 patients (69%), 68% of those in the 5-dose group and 69% of those in the 3-dose group. The two groups did not have significant differences in the number of patients with AEs or serious AEs.

Two patients died, resulting in a mortality rate of 1.1% in the PP population, both in the 3-dose treatment group. One case was a 4-year-old girl who became comatose and died 2 days after admission; this occurred despite decline of parasitemia to 0.3% within 24 hours of admission and clearance by the time of death. The other case was a 34-month old boy who died on day 1, when he developed seizures and respiratory

distress at 10 hours after the first dose of artesunate.

Pharmacokinetic studies showed that children receiving the higher dose regimen of artesunate 4 mg/kg (3-dose regimen) had a slightly slower clearance (0.83 fold; 95% CI, .73–.95; P=.008) for dihydroartemisinin (DHA). The investigators found no associations between the outcome and estimates of pharmacokinetic parameters of artesunate and DHA.

■ COMMENTARY

Artemisinin is a compound that originated from a Chinese herbal plant, *Artemesia annua*, and artesunate is an artemisinin derivative that is effective in treating severe malaria. A Cochrane systematic review that included 8 randomized controlled trials comparing intravenous, intramuscular, or rectal artesunate with intravenous or intramuscular quinine for severe malaria found that artesunate significantly reduced the risk of death both in adults (RR 0.61, 95% CI 0.50-0.75; 1664 participants, five trials) and children (RR 0.76, 95% CI 0.65-0.90; 5765 participants, four trials).[1] An open-label, randomized trial comparing IV artesunate versus quinine in 5425 African children (age <15 years) with severe malaria demonstrated a relative reduction for risk of death 22.5% (95% CI 8.1-36.9; p=0.0022) in the artesunate group.[2]

The dosing of artesunate was derived empirically by the World Health Organization, and subsequently adjusted based on previous clinical trial results to 2.4 mg/kg at hours 0, 12, 24, and then daily for 7 days.[3,4] Kremsner et al aimed at simplifying treatment courses by reducing the number of artesunate doses and achieving rapid parasite clearance without increased drug toxicity. Furthermore, they estimated that the 3-dose regimen could reduce cost by 40%.

A number of factors influence the cost-effectiveness of severe malaria treatment, including drug cost, laboratory tests, IV fluids, hospitalization charges, and estimates of the cost per disability-adjusted life year (DALY) averted and the cost per death averted. Taking into account these factors, IV artesunate and quinine treatments appear to have been similar in the African Quinine Artesunate Malaria Treatment trial that involved >5400 children.[5] The artesunate treatment group had 22.5% lower mortality than the quinine treatment group and both had similar rates of neurological sequelae. Additionally, artesunate showed low incremental cost per DALY averted of US$ 3.8 and an incremental cost per death averted of US$ 123.

The absence of drug-induced hemolysis in this trial provides much reassurance. A retrospective analysis of 25 travelers with severe imported malaria treated with IV artesunate in Europe led to cure in all.[6] Parasitemia responded rapidly to IV artesunate, but hemolysis occurred in 6 patients at 5 centers despite their decline in parasitemia, and necessitated blood transfusion in five patients.[6] Some speculate that the product used to treat the patients in Europe had not met the cGMP guidelines. Hence it is important that the product utilized in this study had been manufactured under cGMP guidelines.

The pharmacodynamics of artesunate are becoming partially clarified although the main pharmacokinetic variables are not consistently related to efficacy.[7,8] IV artesunate appears to be associated with high initial artesunate concentrations that decline rapidly, with estimated half-life of <15 minutes.[8] DHA, the active metabolite of artesunate, reaches peak level within 25 minutes after administration, and is eliminated with a short half-life of 30-60 minutes. Some evidence suggests that pregnancy and acute malaria infection may affect the pharmacokinetics of artesunate and/or DHA following a dose of artesunate.[8]

Kremsner et al found only slightly slower drug clearance in the higher dose (3-dose) treatment, but no associations between pharmacokinetic estimates and clinical outcome. Additional assessments are needed regarding the influences

on the pharmacokinetics of artesunate and DHA and their relationships to artesunate efficacy. Finally, the 3-dose artesunate is found to be comparable to the 5-dose regimen using parasitemia as the end point. The two fatalities that occurred in this trial likely would not have responded to any existing treatments. Nonetheless, extremely severe cases merit detailed analyses to assess the potential for any additional or synergistic treatments. ■

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U.S. Rabies Update: Survival from Rabies, and Death in a Haitian Woman

ABSTRACT AND COMMENTARY

By Michele Barry, MD FACP and Brian G. Blackburn, MD

Dr. Barry is the Senior Associate Dean for Global Health at Stanford University School of Medicine and Dr. Blackburn is a Clinical Assistant Professor in the Division of Infectious Diseases and Geographic Medicine at Stanford University School of Medicine.

Drs. Barry and Blackburn report no financial relationships to this field of study.

Synopsis: *An 8-year-old girl from rural California who had been scratched by unvaccinated cats developed flaccid paralysis and rabies encephalitis. She was treated with a therapeutic coma protocol and survived after a 52-day hospitalization. This is the second report of recovery from rabies after induction of therapeutic coma and the third report of recovery from clinical rabies in an unvaccinated host. A 73-year-old woman who acquired rabies from a dog bite in Haiti died despite intensive supportive care without therapeutic coma induction. Since 1994, nearly all dog-associated rabies cases in the U.S. have been imported, and this was the third case of rabies imported from Haiti since that time.*

Sources:

1. CDC. Recovery of a Patient from Clinical Rabies – California 2011 *MMWR* 2012;61:61-65

2. CDC. Imported Human Rabies – New Jersey 2011 *MMWR* 2012 60;1734-1736

In May 2011, an 8-year-old girl developed sore throat, vomiting, and swallowing difficulties. During two emergency room visits with diffuse abdominal pain, she was given intravenous fluids and diagnosed with a viral illness. During a third emergency room visit for abdominal pain, weakness and sore throat, she was confused and choked while trying to drink radiographic contrast medium for a CT scan. She developed respiratory distress, was intubated and admitted to a pediatric intensive-care unit. She had bilateral lower extremity weakness, and a CSF analysis revealed 6 WBCs, protein 62 mg/dL and normal glucose concentration. Over the next few days she developed ascending flaccid paralysis, fever and decreased consciousness. MRI scanning revealed abnormalities in the periventricular white matter, cortical and subcortical regions. Electromyography revealed a severe demyelinating motor polyneuropathy.

IgG and IgM rabies virus specific antibodies were detected in both her serum and CSF by indirect fluorescent antibody (IFA) testing. With a presumptive diagnosis of rabies, the patient was sedated with ketamine and midazolam, then given amantadine, nimodipine, fludrocortisone, and hypertonic saline. To avoid blunting of an immune response, neither rabies immunoglobulin nor rabies vaccine were administered. Her course was complicated by severe autonomic instability, supraventricular tachycardia and significant hypertension. She was successfully extubated 15 days after hospitalization and discharged 37 days later with a residual foot drop that ultimately resolved. She has no

lasting cognitive impairment.

The girl resided in rural Humboldt County, CA and had not traveled internationally in the six months prior to illness onset. She had never been vaccinated against rabies. Although her family owned pigs, birds, dogs, and a horse, the most likely source of rabies in this case was felt to have been scratches by two different unvaccinated, free-roaming cats at her school 9 weeks and 4 weeks prior to her illness. Although only two cases of human rabies in the U.S. have been attributed to cats since 1960, the most recent rabid cat in California was reported from the same county as the patient's residence, in 2008.

In July 2011, a 73 year-old Haitian woman was admitted to a New Jersey hospital with right shoulder pain, chest pain, headaches and hypertension. When given oral pain medication she developed difficulty swallowing and refused further testing. She then visited two other emergency departments with shortness of breath, ataxia and hallucinations. A blood chemistry panel and head CT were normal, but when she developed incoherence, fever and upper extremity tremors, she was transferred to an ICU where a presumptive diagnosis of encephalitis was made. MRI scanning revealed only chronic periventricular white matter changes; EEG showed subclinical seizures, and CSF revealed 7 lymphocytes/microliter. Rabies virus antigens were detected in a nuchal skin biopsy by direct fluorescent antibody testing, and rabies virus RNA was detected in the biopsy and saliva by PCR testing. Sequencing revealed a rabies virus associated with a Haitian canine variant. She was declared brain dead two weeks after admission and she expired despite supportive care in an intensive care unit. The patient had visited Haiti three months prior to her hospitalization, where she was bitten by a dog that she had adopted. A week before hospitalization, she had complained of right arm numbness and headaches.

■ COMMENTARY

Rabies is a neurotropic viral illness that is characterized by severe encephalopathy and generalized paresis. Although preventable by post-exposure prophylaxis, no proven therapy exists after the onset of clinical symptoms. Post-exposure prophylaxis for unvaccinated patients consists of wound washing, passive immunization with rabies immune globulin and a series of 4 doses of rabies vaccine for immunocompetent hosts[1,2] Survival has rarely been reported after onset of symptoms and death usually occurs within seven to fourteen days, as described in the imported case from Haiti.[2]

The young girl from California is the third unvaccinated person reported to have survived clinically apparent rabies in the United States. In two of these three cases, including the present case, coma induction by what is sometimes referred to as the "Milwaukee protocol" may have been life-saving.[3] Of note, both patients were young and healthy, and presented at an early stage of the disease. A third case of presumptive abortive human rabies that never required intensive care has been described in an adolescent girl from Texas with a history of encephalitis and positive serology after a history of bat exposure.[4] This case was extremely unusual, as case-fatality after onset of symptoms is essentially 100%, and it was suspected that abortive rabies may have occurred because of an exuberant host immune response.

The only suspicious animal contact for the 8 year old girl from California was with free-roaming cats at her school. Inspection of her home found no evidence of bats. The number of rabies cases among domestic animals has declined markedly in the United States, but varies regionally. Rabid cats represent the majority (62%) of reported rabid domestic animals presumably due to fewer cat vaccination laws and free-roaming of cats.[5] In 2010, 303 cats were reported rabid in the US compared with 69 dogs. However, only two cases of human rabies have been attributed to cats since 1960.[5] Risk between cats and dogs varies regionally and on the Texas-Mexico border dogs represent a greater risk. Most of the 303 rabid cats were reported from states where raccoon rabies is enzootic.[5]

For travelers, dogs remain the greatest risk for acquisition of rabies.[1] The history of the 73 year-old woman who had traveled to Haiti, had been bitten by a dog two months prior, and had not sought medical attention is typical for rabies. Since 2000, eight human rabies cases associated with dog bite exposures have been reported in the United States, all acquired abroad. In the developing world, dogs represent a major source of rabies, in contrast to the U.S. where the major reservoir is wild animals, and where 96% of all domestically acquired human rabies infections have been associated with bat rabies virus variants. This is the third U.S. case of rabies related to dog exposure imported from Haiti in recent years.

Rabies is frequently not considered early in the clinical course of affected patients, but clinicians caring for patients with acute progressive encephalitis should always consider rabies in the differential diagnosis. Although there is no standard treatment for rabies once symptoms begin, early diagnosis may allow consideration of experimental interventions in appropriate patients and can also limit secondary exposures, thus minimizing the need for post-exposure prophylaxis [PEP]. The incubation period can vary depending on bite site but is usually 1-3 months.[1] Ante-mortem diagnoses should include laboratory testing of serum, saliva, CSF and a nuchal skin biopsy to optimize yield as these tests have variable sensitivity. Interestingly, neither infectious virus, viral antigens nor rabies viral nucleic acid have been detected in any of the three surviving cases, raising the question of patient survival due to robust immune responses during intensive care support. For this reason, immunization with vaccine and human rabies immune globulin [HRIG] is not recommended once rabies encephalitis has been diagnosed in order to prevent blunting of the immune response.

A major clue to rabies in all of these cases was dysphagia and difficulty swallowing. This significant degree of dysphagia rarely is seen with encephalitis due to other causes. CDC recommends that all domestic cats, dogs and ferrets be vaccinated against rabies. Travelers to countries endemic for rabies should consider pre-exposure rabies vaccination, especially if immediate access to appropriate medical or biologics such as HRIG is limited or whenever the potential of exposure to rabies is high.[1] Even if an animal exposure does

occur, rabies is preventable if post-exposure prophylaxis is administered soon after exposure. In countries where canine rabies is endemic, all dog bites should be managed as a rabies exposure unless the dog's disease-free status can be confirmed. ■

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Cystic Cerebellar Lesions Post Honeymoon: A Strange Case of Neurocysticercosis

CASE REPORT AND COMMENTARY

By Maria D. Mileno MD

Dr. Mileno is the Director, Travel Medicine, The Miriam Hospital and Associate Professor of Medicine, Brown University, Providence, RI.

Dr. Mileno reports no financial relationships to this field of Study

Synopsis: *This case report of a US traveler is paired with a review of neurocysticercosis cases in Israel published in Journal of Travel Medicine illustrating the broad spectrum of clinical presentations that can be encountered with this disease.*

Source: Leshem E, Kliers I, Bakon M et al. Neurocysticercosis in Travelers: A Nation-Wide Study in Israel. *Journal of Travel Medicine*. 2011; 18: 191-197.

Case Summary: A 27- YEAR-OLD PHYSICAL EDUCATION teacher presented with two separate episodes of ill-defined dizziness and mild confusion over a period of one week. He was in good health, except for numerous upper respiratory infections during the months prior to his onset of dizziness. The first episode occurred while he was working in his basement. He described a feeling of "spaceyness" with difficulty forming words. This lasted roughly 90 minutes. He did not lose consciousness. The second episode occurred while he was playing basketball at the school where he is a physical education teacher, and it was quite similar to the first episode. The school nurse evaluated him and found an elevated blood pressure. He was sent by ambulance for hospital evaluation of hypertension and dizziness at which time CT imaging and an MRI revealed cystic cerebellar lesions. He had neither focal neurological symptoms nor fever in association with these episodes, and no nausea nor vomiting. Clinically the episode seemed most consistent with either a seizure aura or a true seizure. Further neurosurgical evaluation excluded a brain tumor, stroke or seizure disorder based upon his clinical examination, an EEG and the MRI appearance [see Fig 1A and 1B] of his lesions. He was referred for an outpatient infectious disease consultation to evaluate these symptoms and for further management of probable neurocysticercosis.

His history included travel to Mexico on his honeymoon 6 months previously, at which time he ate undercooked meat, most likely prepared using the "Mayan methods" in which meat was "wrapped in banana leaves and baked in the earth." He also ate sushi occasionally at the time. He described no acute symptoms immediately after his honeymoon and states that he was at an upscale resort. There was no significant family history and his wife felt well, without any symptoms after the honeymoon. The patient denied tobacco, alcohol or recreational drug use.

An initial CT scan [not shown here] identified 2 small focal defects in the right cerebellum measuring 0.6 and 1.1 cm in diameter. The MRI scan shows the extent of the brain involvement without cerebral lesions. (See Fig 1A and 1B.) Clinically the episode seemed most consistent with a seizure aura or true seizure. (1A). The T2 weighted images showed a focus of five or six rounded areas of bright signal in the right posterior fossa of the cerebellum, the largest measuring approximately 8 mm with an internal nodular septate appearance. Post-gadolinium imaging showed a tiny nodule enhancing at the midparietal level to the right of the midline, not shown in this image.(1B)

Serological tests for cysticercosis were forwarded to the CDC, but given his ongoing symptoms and known risk of brain edema during treatment he was hospitalized for pretreatment with dexamethasone and praziquantel 100 mg/kg/d, in 3 divided doses. He tolerated this well, but required diphenhydramine for skin redness with administration of his praziquantel. He completed 2 weeks of high dose corticosteroids. Almost daily he continued to have episodes of the "strange feeling" he found difficult to describe. Things seem to be "happening fast" and vision during this 10-minute period was less focused. He had to look away then refocus on TV for example. No loss of consciousness occurred. Episodes were sometimes more intense than his original presentation, but similar in nature. Final serological tests,

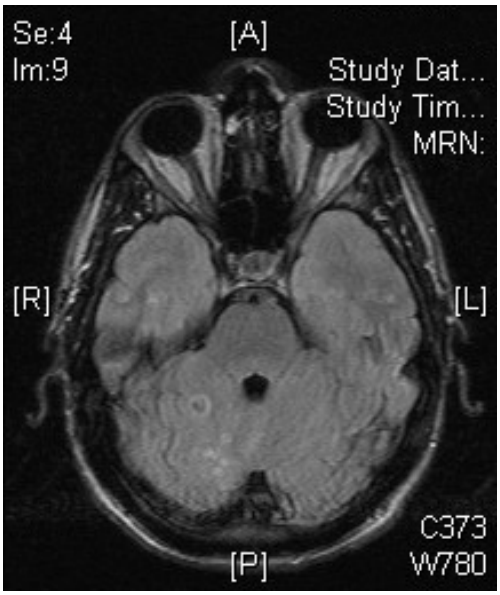

Fig. 1A: MRI scanning and imaging of initial cerebellar lesions

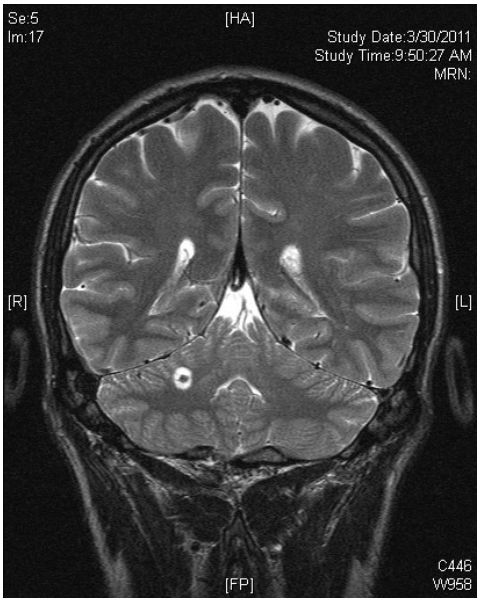

Fig. 1B: MRI scanning and imaging of initial cerebellar lesions

including the Immunoblot assay for cysticercosis antibodies performed at CDC were negative. Upon follow up with the patient 6 months later (See Fig 2) he was well and without further episodes.

The nine Israeli patients with neurocysticercosis described in the *Journal of Travel Medicine* had traveled to South Asia and /or southeast Asia[1] and the most common presenting symptom at the time of diagnosis was a seizure. The average time interval from the suspected travel exposure and the onset of symptoms was 3.2 + 1.8 years. Two patients had multiple lesions; the others had a single lesion, and all were cerebral. Anti-helmintic therapy was given to most of these patients with resolution of symptoms. Antiepileptic treatment was utilized for 16 after albendazole was administered, and was eventually discontinued in all patients without any complications.

Other neurocysticercosis cases reported from Korea and Japan showed that very few had cerebellar involvement. The therapeutic approach ranged from neurosurgical intervention for impending brain herniation, to expectant treatment with steroids and albendazole for 28 days.

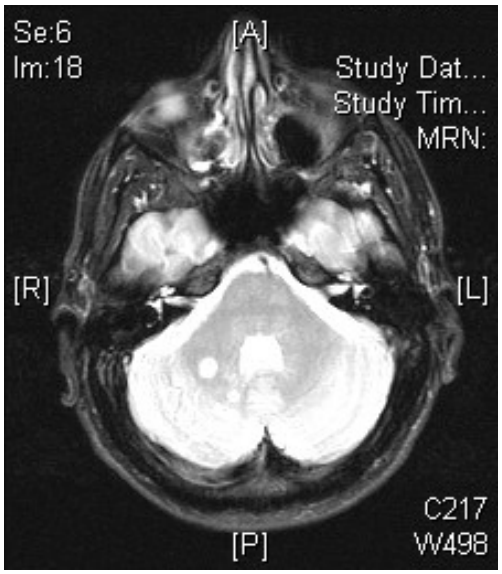

Fig. 2: MRI 6 months post treatment showing calcified lesions in the cerebellum, no new lesions remaining.

■COMMENTARY

Many features of our case were atypical including a presentation with ill-defined symptoms, the presence of lesions predominantly located in the cerebellum and the lack of confirmatory serology for cysticercosis. It was fortunate that a travel history was obtained and led to a consideration of neurocysticercosis in this patient. It is truly amazing to think that an upscale resort might convince honeymooners and others that eating in the dirt is probably safe!

Parasite immune evasion of the host immune system is one explanation why viable cystic neurocysticercosis lesions generally do not cause inflammation and are commonly asymptomatic.[2] Parasite death leads to a breakdown of this protective mechanism and results in a profound inflammatory reaction; this can cause an encephalitic syndrome and clinical deterioration in patients who have primarily cerebral lesions. It can be provoked by cysticidal therapy.

An overriding concern that he might have had significant cerebellar inflammation and edema during degradation of the parasite and potentially herniate during treatment prompted me to initiate treatment in the hospital under observation with neurosurgical assistance available. He improved clinically, and the lesions evolved over six months into a calcified appearance, yet the case remained unsettling during that time.

Single-day praziquantel treatment regimens with favorable results have been published. They allowed us to com-

plete anti-parasitic treatment during a short inpatient stay, followed by a prolonged course of cortiosteroids for two additional weeks to produce continued eradication of the parasites.

The paper by Leshem et al offers numerous references that explore the magnitude of neurocysticercosis as an emerging infection, and the various approaches to disease management in the summaries of case reports. The spectrum of treatment options has ranged from no treatment to neurosurgery and a panel of experts wrote consensus guidelines to set some basic principles of therapy.[3] They concluded that each case must be individualized. Anti-parasitic agents should not be used in those cases showing already calcified parasites or during cysticercosis encephalitis. Importantly, antiparasitic treatment should be used to treat actively growing cysts and pre-treatment corticosteroids should be utilized, as well as anti-seizure medications. A growing lesion may require surgical excision. Cysts located in the ventricular system should be treated surgically if the necessary neuroendoscopic techniques are available. When hydrocephalus or intracranial hypertension is present management using a ventricular shunt is the top priority.

We had the benefit of follow-up neuroimaging technique. On a worldwide basis this may not be available nor performed for economic reasons. There are no studies showing long-term outcomes for neurocysticercosis. This case, in conjunction with the series published by Leshem et al, provides follow up that should be reassuring about the favorable course of this disease with medical management.[4] ■

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Dengue in Pediatric Travelers

ABSTRACT AND COMMENTARY

By Philip R. Fischer, MD, DTM&H

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Dr. Fischer reports no financial relationships to this field of study.

Synopsis: *Dengue fever occurs in children traveling to visit friends and relatives in a pattern similar to what is seen in children living in endemic areas. Careful attention to pre-travel counsel about insect bite prevention is warranted.*

Source: Krishnan N, et al. Severe dengue infection in pediatric travelers visiting friends and relatives after travel to the Caribbean. *Am J Trop Med Hyg* 2012;86:474-476.

A RETROSPECTIVE REVIEW OF PEDIATRIC CASES OF DENGUE FEVER was undertaken at a single health center in the Bronx area of New York. Over a 3 ½ year period, eight children with dengue infection were identified. Each child had traveled to the Caribbean (seven to the Dominican Republic, one to Puerto Rico), and the duration of their trips ranged from ten days to four years. Care was sought within 11 days of returning to New York. Each affected child presented with fever, and most indicated both gastrointestinal complaints and myalgia. Leukopenia and thrombocytopenia were common, and half showed ascites that was visible on abdominal ultrasonography. Three (38%) of the children had complicated courses, two with dengue hemorrhagic fever and one with dengue shock syndrome. With treatment, each child recovered fully.

Many of these children, including both of those with dengue hemorrhagic fever, had serologic evidence of having also had a previous dengue infection. However, a child with dengue shock syndrome was eight months old and experiencing a primary dengue infection.

■ COMMENTARY

Even as malaria is receding from some areas of the world, dengue infections are spreading geographically and becoming increasingly common.[1] Imported dengue is increasingly identified both in North America1 and Europe.[2]

Dengue is transmitted by the bites of Aedes mosquitoes that are well-adapted to urban environments.[3] These mosquitoes will bite humans who are either indoors or outdoors, and they often feed during daylight hours. These vectors are "nervous" feeders that can interrupt blood meals and then restart another meal on a nearby individual, thus resulting in multiple infections in the same household at the same time.[3,4]

Four distinct serotypes of dengue virus cause human infection.[4] Typically, severe disease occurs in individuals who have also had previous dengue infection with a different dengue serotype. It is thought that antibody enhancement of the second infection superimposed on existing sero-specific immunity triggers an exaggerated cytokine response with capillary leak and severe illness.[4,5] Interestingly, as seen in this new report from the Bronx and in pediatric populations in dengue-endemic areas, the dengue shock syndrome form of illness is often seen in infants during the second half of the first year of life. Perhaps this is due to interactions between the child's primary dengue infection and waning maternal antibodies that had been acquired transplacentally. Another recent report, however, revealed that adult travelers could have significant ultrasonic evidence of capillary leakage

even with primary dengue infection that presented without severe illness.[6]

This report from the Bronx highlights the importance of providing pre-travel guidance to individuals and families who make repeated visits to dengue-endemic areas. Mosquito avoidance measures must be emphasized. ■

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CME Objectives & Instructions

Upon completion of this educational activity, participants should be able to:

- discuss the latest data regarding the diagnosis and treatment of various travel-related diseases;
- explain new data concerning recommended precautions and prophylaxis for patients traveling to specific areas of the world;
- implement strategies in the practice setting to inform patients of disease outbreaks and epidemics relevant to their travel plans.

To earn credit for this activity, please follow these instructions.

1. Read and study the activity, using the provided references for further research.
2. Log on to www.cmecity.com to take a post-test; tests can be taken after each issue or collectively at the end of the semester. First-time users will have to register on the site using the 8-digit subscriber number printed on their mailing label, invoice or renewal notice.
3. Pass the online tests with a score of 100%; you will be allowed to answer the questions as many times as needed to achieve a score of 100%.
4. After successfully completing the last test of the semester, your browser will be automatically directed to the activity evaluation form, which you will submit online.
5. Once the completed evaluation is received, a credit letter will be e-mailed to you instantly.

CME Questions

1. Artesunate [intravenous] for therapy of malaria:
   A. is recommended by the World Health Organization for uncomplicated malaria
   B. achieves more rapid parasite clearance compared to intravenous quinine
   C. costs an exorbitant amount and is unaffordable for most malaria endemic countries
   D. requires several days of therapy to reach peak drug concentration which declines quickly thereafter

2. The syndrome and disease pattern referred to as dengue fever:
   A. is rare in children under 10 years of age
   B. is increasing in frequency
   C. is most severe in previously unexposed individuals without immunity
   D. is acquired after nighttime bites by Anopheles mosquitoes

3. Most cases of central nervous system are characterized by:
   A. diffuse cerebellar involvement on MRI scanning
   B. calcified lesions that require follow up anti-parasitic treatment
   C. spinal cord involvement, in addition to cerebral lesions, when imaging studies are performed
   D. failure to respond to anti-parasitic therapy unless accompanied by use of corticosteroids
   E. None of the above

PHARMACOLOGY WATCH

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

Statins and the Risk of Diabetes

In this issue: Statins and diabetes risk; new treatment guideline for diabetes; new pertussis vaccine recommendation; antibiotics and rhinosinusitis; fluoroquinolones and cystitis; and FDA actions.

Do statins increase the risk of diabetes?

Studies have suggested that statins may increase the risk of diabetes in the elderly, women, and Asians. A new study reviews data from the 162,000 postmenopausal women enrolled in the Women's Health Initiative to investigate whether the incidence of new onset diabetes mellitus (DM) is associated with statin use among these women. This study reviewed records from women who were enrolled between 1993 and 1998 through 2005. More than 7% of the women in the study reported taking statins. Statin use at baseline was associated with an increased risk of DM (hazard ratio, 1.71; 95% confidence interval, 1.61-1.81). This association remained after adjusting for other potential confounders, including obesity, and was observed for all types of statin medications. The authors conclude that statin medication use in postmenopausal woman is associated with an increased risk for DM and that this may be a medication class effect (*Arch Intern Med* 2012;172:144-152). As pointed out in a brief comment in the same issue, observational data are potentially susceptible to "bias (confounding) by indication." In other words, women who would be prescribed statins may be inherently at risk for DM. This study did a good job of evaluating women with and without a history of cardiovascular disease and found that there was still an increased risk of DM. This finding "may have important implications for the balance of risk and benefit of statins in the setting of primary prevention in which previous meta-analyses show no benefit on all-cause mortality." The FDA has issued a new warning about statins and the risk of diabetes (see FDA actions). ■

Oral medications for diabetes

The American College of Physicians has published a new guideline for the "Oral Pharmacologic Treatment of Type 2 Diabetes Mellitus" in the February 21 issue of the *Annals of Internal Medicine*. The guideline suggests that if diet, exercise, and weight loss fail to improve hyperglycemia, oral drug therapy should be initiated. Most diabetes medicines lower HbA_{1c} levels to a similar degree, and none of the medications have compelling outcomes data to suggest one class is superior to another class with regard to cardiovascular or all-cause mortality. But metformin "was more effective than other medications as monotherapy as well as when used in combination therapy with another agent for reducing HbA_{1c} levels, body weight, and plasma lipid levels (in most cases)." Therefore, the guideline recommends that clinicians prescribe monotherapy with metformin for initial pharmacologic therapy for most patients with type 2 diabetes. Metformin is effective at reducing glycemic levels and is not associated with weight gain. Additionally, the drug helps reduce LDL cholesterol and triglyceride levels. Metformin is contraindicated in patients with impaired kidney function, decreased tissue perfusion or hemodynamic instability, liver disease, alcohol abuse, heart

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failure, and any conditions that might lead to lactic acidosis. For patients with persistent hyperglycemia despite metformin, a second drug should be added. No good evidence supports one combination over another. Sulfonylureas have a higher risk for hypoglycemia and thiazolidinediones are associated with an increased risk for heart failure. There are no specific recommendations for the use of the glinides (nateglinide or repaglinide) or the DPP-4 inhibitors (linagliptin, saxagliptin, or sitgliptin). The guideline does not make a recommendation for combinations of more than two oral agents. Injectables, such as the various insulins and GLP-1 analogs, were not addressed in the guideline. (*Ann Intern Med* 2012; 156:218-231). ■

New recommendation for Tdap vaccine

The Advisory Committee on Immunization Practices, a division of the Centers for Disease Control and Prevention, is recommending that all adults get immunized against pertussis (whooping cough). Previously the committee had recommended that only adults who spend time around infants or young children should be immunized. The goal of the expanded recommendation is to prevent teenagers and adults from spreading the disease to infants. In 2010, California experienced a pertussis outbreak that infected 9000 people and resulted in 10 infant fatalities. The adult vaccine combines tetanus, diphtheria, and acellular pertussis (Tdap). ■

Antibiotics not needed for rhinosinusitis

Physicians now have more ammunition for not treating patients with acute rhinosinusitis with antibiotics, based on the results of a new study that shows amoxicillin is of no benefit in these patients. Researchers at Washington University in St. Louis randomized 166 adults with uncomplicated, acute rhinosinusitis to a 10-day course of amoxicillin 500 mg three times a day or matching placebo. The main outcome (change in the Sinonasal Outcome Test) was not significantly different between the two groups at day 3 or day 10. There was a slight improvement in the antibiotic group at day 7. The authors conclude that "treatment with amoxicillin for 10 days offers little clinical benefit for patients clinically diagnosed with uncomplicated acute rhinosinusitis." Patients with symptoms indicative of serious complications were excluded from the trial (*JAMA* 2012;307:685-692). ■

Fluoroquinolones for cystitis

Cefpodoxime is inferior to ciprofloxacin for short-course treatment of acute uncomplicated cystitis in women, according to new study. In a randomized, double-blind trial, 300 women ages 18-55 with uncomplicated cystitis were randomized to ciprofloxacin 250 mg orally twice daily for 3 days or cefpodoxime 100 mg twice daily for 3 days. The overall clinical cure rate with the intent-to-treat approach in which patients lost to follow-up were considered as having a clinical cure was 93% for ciprofloxacin compared to 82% for cefpodoxime. For the intent-to-treat approach in which patients lost to follow-up were considered as not having responded to treatment, the clinical cure rate was 83% for ciprofloxacin compared to 71% for cefpodoxime. The microbiological cure rate was 96% for ciprofloxacin compared with 81% for cefpodoxime. At follow-up, 16% of women in the ciprofloxacin group had vaginal *Escherichia coli* colonization compared with 40% in the cefpodoxime group. The authors conclude that cefpodoxime did not meet criteria for non-inferiority to ciprofloxacin for treating uncomplicated cystitis in women (*JAMA* 2012;307:583-589). The study is somewhat disappointing given the increasing rates of fluoroquinolone resistance in the community and the need for effective alternatives. ■

FDA actions

The FDA has issued a new warning and is requiring label changes to all statins regarding the risk of elevated blood sugar and reversible cognitive changes. The agency is making these changes after a comprehensive review of multiple studies that show increases in blood sugar associated with the drugs. A separate labeling change warns that cognitive effects have been reported with statin use, including transient memory loss and confusion — symptoms that are reversible with stopping the medication. There is no evidence that statins are associated with long-term cognitive changes or dementia. Statins affected by these warnings include atorvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin, and simvastatin. In a separate warning, lovastatin is now contraindicated with strong CYP3A4 inhibitors, such as itraconazole and erythromycin. This is a similar warning to that issued for simvastatin in 2011.

In one of the strangest stories of the year, the FDA is warning oncologists that a counterfeit version of bevacizumab (Avastin) may have been purchased and used by some medical practices in the United States. The counterfeit version does not contain any active drug and may have resulted in patients not receiving needed therapy. Counterfeit bevacizumab was purchased from a foreign supplier known as Quality Specialty Products or Montana Health Care Solutions. The FDA is recommending that physicians stop using bevacizumab purchased from the suppliers and call the FDA immediately. ■