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Behavioral Outcomes in Internationally Adopted Children

ABSTRACT & COMMENTARY

By Chad Lowe, MD, and Philip Fischer, MD, DTM&H

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Drs. Lowe and Fischer report no financial relationship relevant to this field of study.

Synopsis: *International adoption is increasingly popular, but there are still concerns about behavioral outcomes in foreign-born adoptees. In a study of 1,948 such children, behavioral problems were more often seen in boys, in children who had been institutionalized, in those who were adopted after 2 years of age, and in children originating from Eastern Europe and Russia.*

Source: Gunnar MR, van Dulmen MH, International Adoption Project Team. Behavior problems in postinstitutionalized internationally adopted children. *Dev Psychopathol* 2007. 19(1):129-148.

While international adoption increases in popularity, many people remain concerned about potential long-term developmental problems in adopted children. Gunnar and colleagues studied nearly 2,000 institutionalized foreign children (defined as having spent at least 75% of their lives in an institution) who were adopted into the State of Minnesota over a 9-year period, and compared their behavior to that of foreign, adopted children who spent little or no time in institutions prior to adoption (less than 4 months). Data were collected from parents who completed a Child Behavior Checklist (CBCL). It was correctly predicted that institutionalization would be associated with increased risk of attention problems, and not with internalizing (withdrawn, somatic complaints, anxiety or depression) or externalizing (delinquency or aggression) behaviors. Data were further analyzed by age of adoption and location of adoption (Russia or Eastern Europe, in comparison to other areas).

Barely half (51%) of institutionalized children were "problem free" (not scoring in any clinically abnormal range) vs 65% of the control (non-institutionalized) group ($P < 0.001$), and previously institutionalized children were more likely (11% vs 5% respectively, $P < 0.001$) to show pervasive problems (scoring in the clinically diagnostic range across 5 or more domains). Institutionalization did not predict an increased rate of internalizing or externalizing problems per se; however, older age at adoption (greater than 24 months) was universally associated with increased problems across all domains assessed with the CBCL. A gender difference was noted with boys expressing higher rates of behavior problems than girls. Children from Eastern Europe and Russia also

had higher rates of behavior problems than children adopted from other countries.

COMMENTARY

International adoption is an ever increasing means of creating a family, and thousands of American families do so each year. Media reports depicting the plight of children in poor, developing countries evoke strong emotions, and celebrities publicly discuss their international adoptions in the context of social and political problems of specific countries.

Anecdotal accounts exist of adopted children who, in multiple developmental and behavioral domains, fall significantly behind their peers. It has been estimated that over 80% of the nearly 23,000 children who were adopted into the United States in the year 2003 spent some time in an institutional setting prior to adoption. Gunnar's study shows that slightly more than half of adopted children did *not* have significant behavioral problems.

Given press reports of deplorable conditions and horrific circumstances some internationally adopted children experience, one might have predicted an even greater number of behavioral problems in institutionalized children. Gunnar's study underscores the resiliency and plasticity of young children, especially under the age of 24 months. Other research has shown that adoption leads to incredible improvements in multiple domains, including physical growth, cognitive development and school performance, and attachment security.[1]

Counterintuitively, Gunnar's study found that time spent with the adoptive family was associated with increasing behavior problems. It was hypothesized that behavior problems may increase as these children grow older secondary to other factors, such as discrimination associated with race and minority status or lack of coping mechanisms to negotiate increasingly complex peer and social interactions. In addition, adoptive parents may be less likely to believe that problematic behavior is normal as the child grows older. While it is possible that an adoptive family environment may contribute to behavioral problems, many known familial factors that lead to behavior problems, such as poverty and divorce, were not present in the group studied. Other investigations have shown that, in general, parental responsiveness and sensitivity to adoptive children improve over time.

After the Vietnam war, Korean conflict, and the fall of Communism, we were made aware of children who otherwise fell victim to disease and neglect. With the current AIDS epidemic in Africa, adoption has again been proposed as an option to help curb the number of abandoned orphans when other options (such as kinship and intracountry adoptions) have been exhausted.[2]

International adoption often creates mixed-race families, which can add unique and unanticipated challenges to the post-adoptive adjustment period. A recent study showed that many adoptive parents with "color-blind" racial attitudes actively spoke to their children and others, such as school teachers, about racism and discrimination and pursued cultural activities.[3]

Adopting children from third world nations with substandard health care adds an additional dimension to caring for newly adopted children. Parents and families who travel to escort their new children home are at risk for contracting infectious diseases and require pre-travel

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medical counseling.[4, 5] A small study of children who had been hospitalized prior to adoption in Sweden showed MRSA carriage of 54% and subsequent transmission of MRSA to adoptive family members occurred.[6] Many children arrive in their adoptive families with little or no medical records or with illnesses rarely seen in industrialized nations.[5] A recent study of adoptive children who presented to a travel clinic in Nepal had common medical conditions, but were rarely up to date with immunizations or did not have valid documentation of immunizations.[4]

As international adoption increases in popularity, travel medicine practitioners will continue to provide pretravel consultation to families traveling overseas to pick up children. At the same time, they might be called on to provide counsel about expectations for developmental outcomes in adopted children. While most foreign-born adoptees do very well, behavioral and developmental difficulties are more common in children who were institutionalized prior to adoption, in those who were adopted after 2 years of age, in boys, and in children from Eastern Europe and Russia. ■

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Fluoroquinolones No Longer Recommended for Gonorrhea

ABSTRACT & COMMENTARY

By Mary-Louise Scully, MD

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Dr. Scully reports no financial relationship relevant to this field of study.

Synopsis: *On the basis of surveillance data showing a significant rise in fluoroquinolone resistance, the CDC has issued a new update removing fluoroquinolones from the recommended options for the treatment of gonococcal infections.*

Source: CDC. Update to CDC's Sexually Transmitted Diseases Treatment Guidelines, 2006: Fluoroquinolones No Longer Recommended for Treatment of Gonococcal Infections. *MMWR Morb Mortal Wkly Rep* 2007:56:332-336.

Since 1993, oral quinolones (ciprofloxacin, ofloxacin, and levofloxacin) have been recommended by the CDC as first-line treatments for gonorrhea. The Gonococcal Isolate Surveillance Project (GISP) monitors trends in the development of antimicrobial resistance of *Neisseria gonorrhoeae* in the United States. Throughout most of the 1990s the prevalence of fluoroquinolone-resistant *N. gonorrhoeae* (QRNG) remained at less than 1%, but in 2000, based on rising resistance rates, fluoroquinolones were no longer recommended for gonorrhea treatment in persons who acquired their infections in Asia or the Pacific Islands (including Hawaii). In 2002, this recommendation was extended to California and more recently (2004) to men who have sex with men (MSM). Recommendation changes are made when QRNG prevalence exceeds 5% in defined groups or locations. Both the CDC and the WHO have used this 5% threshold so that all recommended treatment regimens for gonorrhea can be expected to cure >95% of infections.

By June of 2006, the QRNG prevalence had increased to 38.3% among MSM and 6.7% among heterosexual men. Therefore, on April 12, 2007, the CDC announced that fluoroquinolones were no longer recommended for the treatment of gonorrhea in the United States.

Options for treating gonorrhea are now limited to a single class of antibiotics, cephalosporins. Ceftriaxone, given as a 125 mg intramuscular (IM) dose, remains the preferred treatment for many types of gonorrhea infection (genital, anal, and pharyngeal). A single oral dose of cefixime 400 mg can also be used for uncomplicated urogenital and anorectal gonorrhea, but cefixime does not appear to be adequate for treating the more difficult to eradicate pharyngeal infections. However, in the United States the 400 mg cefixime tablets are not available, although there is a suspension formulation. Other parenteral single dose regimens for uncomplicated urogenital and anorectal gonorrhea (ceftizoxime 500 mg IM; cefoxitin, 2 g IM with 1 g probenecid orally; or cefotaxime 500 mg IM) remain options though they do not appear to offer any advantage over ceftriaxone.

A single oral dose of azithromycin 2 g is effective against uncomplicated gonococcal infections from any

site, but due to concerns that widespread use will result in more rapid emergence of resistance, this option should be reserved for persons with documented severe-allergic reactions to penicillins or cephalosporins.[1]

Patients diagnosed with gonococcal infections should be treated for possible coinfection with Chlamydia trachomatis if chlamydial infection has not been ruled out. Either doxycycline, 100 mg twice a day for 7 days, or azithromycin 1 g by mouth are acceptable regimens.

COMMENTARY

Gonorrhea is the second most commonly reported infectious disease in the United States with over 330,000 cases reported in 2004.[2] *N. gonorrhoeae* infections are important causes of urethritis, cervicitis, pelvic inflammatory disease, and less frequently may cause of pharyngitis, proctitis, and disseminated disease. Reported cases likely underestimate the number of people truly infected and long-term sequelae such as infertility, ectopic pregnancy, and chronic pelvic pain can result from previous gonorrhea infection. Rarely, untreated gonorrhea may be associated with serious sequelae such as infectious arthritis, meningitis, or endocarditis.

Treatment is challenging because of the ability of *N. gonorrhoeae* to develop resistance to antimicrobial therapies. Recent reviews of published literature on the global prevalence of QRNG shows high prevalence of QRNG in Europe, Central and southeast Asia, and the South Pacific.[3] In many areas of South America and Africa there are insufficient surveillance data available to assure that quinolones are still effective. The United Kingdom preceded the United States by 3 to 4 years in recommending the switch from fluoroquinolones to cephalosporins for gonorrhea treatment.

Quinolones for gonorrhea treatment were single-dose oral regimens that improved compliance and were relatively affordable in a variety of health care settings. Treatment of sexual partners, when appropriate, was also readily accomplished using these single-dose oral options. The development of fluoroquinolone resistance has now eliminated these as recommended drugs regimens. With cephalosporins now being the only class of drugs for gonorrhea treatment, we will need vigilance about monitoring for the possible emergence of cephalosporin resistance. The new updated guidelines including recommended treatments regimens for disseminated gonococcal disease, pelvic inflammatory disease, and disease during pregnancy can be accessed at www.cdc.gov/std/treatment. Clinicians and laboratories should report treatment failures or resistant gonococcal isolates to CDC at (404) 639-8373 through state and local public health authorities. ■

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Relapses of *Plasmodium vivax* Infections

ABSTRACT & COMMENTARY

By Lin Chen, MD

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Dr. Lin H. Chen reports no financial relationship relevant to this field of study.

Synopsis: *The majority of* P. vivax *relapses appear to be caused by activation of hypnozoites distinct from original infections. At times,* P. vivax *relapses may not be effectively treated with chloroquine and primaquine, particularly tropical strains. Better ways to predict and treat relapses are needed.*

Sources: Imwong M, et al. Relapses of *Plasmodium vivax* infection usually result from activation of heterologous hypnozoites. *J Infect Dis* 2007;195:927-933.
Chen N, et al. Relapses of *Plasmodium vivax* infection result from clonal hypnozoites activated at predetermined intervals. *J Infect Dis* 2007;195:934-941.

IMWONG ET AL COLLECTED PAIRED BLOOD SAMPLES from 149 patients with vivax malaria in Thailand (n=36), Myanmar (n=75), and India (n=38), and compared parasite genotypes. The investigators amplified 2 antigenic markers and their results show that the majority of recurrent infections were caused by parasites that were genetically distinct from the *P. vivax* that caused the acute infections.

Among the 36 patients from Thailand in whom reinfection was excluded and recrudescence was considered unlikely, 78% of *P. vivax* parasites causing relapses were determined to be novel populations. Among the 75 patients from Myanmar and 38 patients from India, 75% and 63% of the parasites causing the recurrent infections respectively were such novel populations. The investigators conclude that heterologous hypnozoites of *P. vivax* are activated to cause the first relapses of vivax malaria.

Chen et al analyzed the patterns of relapse and molecular characterization of parasites collected from 71

Australian Defense Force personnel who presented with relapses of vivax malaria after exposure in East Timor. Six patients presented with clinical malaria in East Timor and had relapses after returning to Australia, and 3 had a second relapse. Sixty-five patients had their initial vivax attack after returning to Australia, including 13 patients with 1 relapse, 5 patients with 2 relapses, and 2 patients with 3 relapses. The 71 patients had relapse after presumptive anti-relapse therapy with primaquine, and 27% experienced a second relapse after chloroquine and primaquine (30 mg daily for 14 days). Furthermore, *some relapses occurred more than 300 days after returning to Australia*: 17% of the patients who had malaria attacks in East Timor and 6.8% of the patients who presented with initial malaria attacks in Australia.

Investigators genotyped the parasites and a comparison of 15 paired relapse samples found that among patients with >1 relapse, 71% demonstrated clonal allelic types that differed between the relapses. The investigators concluded that the activation of a single allelic type of hypnozoite causes each relapse. A mathematical model used to test the hypothesis that the hypnozoites operated under a biological clock found the model simulation to correlate with the temporal pattern observed in the malaria attacks.

COMMENTARY

P. vivax and *P. ovale* are Plasmodial species that produce hypnozoites, or dormant liver stages, that can manifest themselves clinically a long time after exposure and infection. *P. vivax* causes >75 million infections globally every year. *P. vivax* infections are usually considered less severe than those caused by *P. falciparum*. However, many severe complications have been reported. Outside of Africa, *P. vivax* causes >50% of malaria infections.[1] The majority of vivax cases outside of Africa (80-90%) occur in Asia, the Middle East and the Western Pacific, and only 10-15% in Latin America. Although *P. falciparum* is predominant cause of malaria in Africa, *P. vivax* may cause up to 20% of malaria cases in Ethiopia and other parts of eastern and southern Africa, and Madagascar. Among reported cases of malaria in the United States from 2001-2004, almost all in travelers, *P. vivax* caused about 25% and *P. ovale* caused 2-4%.[2,3] The proportion of malaria cases caused by *P. vivax* increases to 63-74% in Australia (Brisbane, Melbourne)[4,5,6] reflecting the frequency of travel by Australians to vivax-dominant destinations in Asia.

The current first-line malaria chemoprophylaxis agents (chloroquine, mefloquine, doxycycline, atovaquone-proguanil) are active against blood stages. Use of these agents merely delays the first clinically apparent attack of malaria parasites, but does not prevent relapses caused by *P. vivax* and *P. ovale*. Primaquine is the only available antimalarial that is effective against hypnozoites. Although atovaquone-proguanil may have some activity against the liver stage of *P. vivax*, it does not reliably prevent vivax malaria relapse.[7,8,9] In addition, resistance of vivax malaria to chloroquine has now been well documented.[10,11]

The biology of vivax malaria relapse remains poorly understood. The studies by Imwong et al and Chen et al involved relatively few patients, but are important in elucidating the biology of hypnozoites. To summarize the main points: 1) Each mosquito bite probably introduces multiple sporozoites that are genetically different from each other. 2) Some parasite genotypes seem to be capable of causing both primary attacks and relapses 3) Most *P. vivax* relapses appear to be caused by hypnozoites that are genetically distinct from the parasites causing the initial malaria episode. 4) The hypnozoites seem to be activated on a predetermined schedule. These findings may lead to ways to predict relapses, identify parasites that may cause relapses, and inactivate hypnozoites before they cause relapses.

Chen et al also documented multiple relapses and that such relapses can occur many months or years after the initial malaria infection. Since travelers and clinicians may be less likely to consider malaria when symptoms occur long after travel, travel medicine specialists need to inform patients traveling to areas with significant risk for *P. vivax* to consider this possibility. Patient education material would be helpful to bring awareness to the latency of *P. vivax* infections.[12] Finally, the relapses after presumptive anti-relapse therapy with primaquine following treatment using chloroquine and primaquine illustrate the tolerance of tropical strains of *P. vivax* to primaquine. ■

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Fever and High-Grade Parasitemia Following Splenectomy

CASE REPORT

By Shaili Gupta, MD and Carlos Torres-Viera, MD

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Drs. Gupta and Torres-Viera report no financial relationships relevant to this field of study.

A 59-YEAR-OLD MAN WAS ADMITTED TO THE HOSpital in July 2006, with a 10-day history of fevers, malaise, muscle aches, back pain and progressive weakness. Two days prior to admission, he had developed slurred speech and jaundice .

His past medical history was significant for glioblastoma multiforme of right temporal lobe, which had been treated with surgical resection, chemotherapy and external beam radiation. He underwent a splenectomy 4 years previously for treatment of hypersplenism. He lived in eastern Connecticut and over the previous 2 months, had spent a significant amount of time with his dogs in the backyard.

On physical examination, his temperature was 101.1°F, pulse 106 bpm, and blood pressure 110/57 mm Hg. Skin exam did not reveal a rash, sclera were icteric, lungs were clear to auscultation, heart sounds were tachycardic without any murmur, and abdomen was soft and nontender with a moderately enlarged liver. He was somnolent and confused, with slurred speech, but without other focal neurological deficits or signs of meningeal irritation. Laboratory findings were impressive for thrombocytopenia, leukocytosis, acute renal failure, hyperbilirubinemia, metabolic acidosis, and high serum LDH, creatine kinase, and liver enzymes. Peripheral blood smear revealed intra- and extraerythrocytic. Babesia with 60%-75% parasitemia (Figure 1).

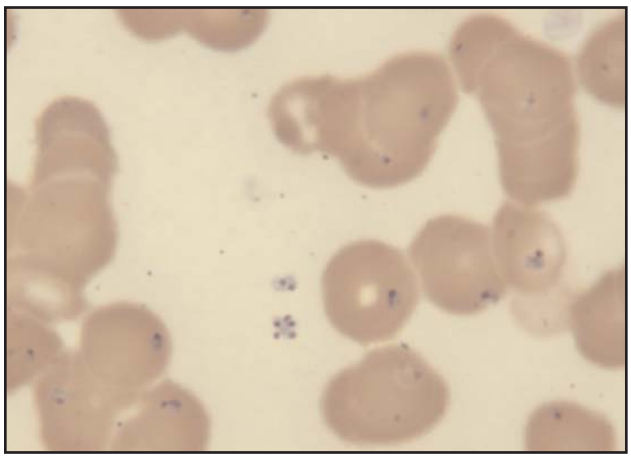

Figure 1. Peripheral blood smear showing high-grade parasitemia (60-75%).

The patient was admitted to the intensive care unit, and started on clindamycin, quinine and doxycycline. Ceftriaxone was given until Lyme serologies were found to be negative. Exchange transfusion was performed within 2 hours of admission with a fall of the parasitemia to 2%. Clinical response was evident by improvement in mental status, resolution of myalgias and defervescence. Laboratory values also improved. Serology and blood smears for Ehrlichia species remained negative. Viral hepatitis serologies, VDRL, CMV Ag, EBV IgM, CMV Ag, Parvovirus B19 IgM and HIV were negative.

On hospital day 5, he developed hyperexcitability, delirium, nausea, vomiting, followed by extreme somnolence. He was found to be persistently hypoglycemic (blood glucose 32-55 mg/dL) despite continuous intravenous glucose infusion. Electrocardiogram revealed prolonged Q-T intervals (433-439 msec). Quinine toxicity was suspected. Therapy was changed to atovaquone and azithromycin with subsequent improvement of symptoms and dysglycemia. Doxycycline was continued. On day 8, fevers recurred (101-102°F) with confusion, myalgias, diarrhea, and mild coagulopathy (INR 1.87). The level of babesia parasitemia increased to 10%. Exchange transfusion was repeated with reduction of parasitemia to <1%. Azithromycin dose was increased to 500 mg daily and he was continued on atovaquone and doxycycline for triple-drug therapy of

babesiosis. Progressive rise in liver enzymes, especially alkaline phosphatase was noted with a value of 748 U/liter on hospital day 25. Right upper quadrant ultrasonography revealed biliary sludge. Azithromycin was discontinued, as a likely cause of cholestasis, and the patient was restarted on clindamycin (atovaquone and doxycycline were continued) with resolution of his cholestatic picture. The patient showed resolution of his symptoms and was discharged home on hospital day 29 taking a triple-antibiotic regimen. His Babesia PCR test remained positive and he was continued on treatment for a total of 60 days when given his persistently negative blood smear his treatment was discontinued. Ten months after the initial diagnosis, the patient remains asymptomatic. Repeated peripheral smears have not shown any evidence of ongoing Babesia parasitemia.

COMMENTARY

B. microti typically causes a subclinical or mild illness characterized by malaise, fever, anorexia, myalgias, and headache. In most instances, specific therapy is not required. In asplenic or immunocompromised patients, however, illness may be severe, with hemolytic anemia, renal dysfunction, and pulmonary involvement. With subclinical infection being the rule, blood transfusions have become an important means of transmission. *B. microti* has been shown to have a tropism for mature erythrocytes[1-3] as reticulocytes do not readily take up the parasite. This may be one reason why asplenic patients, who have impaired destruction of mature RBCs, are more susceptible to severe infections.

The most reliable and definitive diagnostic test is direct visualization of parasitized red blood cells. With low-grade parasitemia, closer inspection of multiple blood smears is usually required to locate a few infected erythrocytes. Once treatment is initiated, many of the intraerythrocytic inclusions may represent nonviable parasites. Elevation of IgM and IgG antibodies against Babesia may be found in acute phase sera followed during convalescence. PCR detection of *B. microti* was initially described as a diagnostic method in 1992.[4] In 1996, a double blind study comparing PCR with blood smear and inoculation of small animals was conducted on 41 asymptomatic participants who lived in an endemic region, and 19 patients were diagnosed with acute babesiosis based on clinical features and serological assays.[5] The sensitivity of thin blood smear, hamster inoculation and PCR were 84%, 74% and 95% respectively and the specificity for all 3 was 100%.[5] However, PCR can remain positive even after clearance of parasitemia and resolution of symptoms. This has been thought to potentially represent viable subclinical infections based upon a prospective study on 46 Babesia-infected subjects, 22 of whom received treatment, while 24 did not.[6] *B. microti* DNA persisted for more than three months in 25 percent of the untreated subjects , but in none of the treated subjects. IgG antibody and subjective symptoms also persisted longer when babesial DNA could be detected by PCR.

In our patient, both symptoms and antibody levels correlated more closely to the parasitemia clearance, than the detection of babesial DNA by PCR. The persistently positive PCR in our patient, in the absence of symptoms and with declining antibody titers, likely represented the detection of nonviable DNA by PCR. Diagnosis of acute as well as persistent or relapsed babesiosis must incorporate clinical assessment along with any of the common diagnostic modalities, including blood smears, PCR and serology,.

The treatment of Babesia infections is based on a combination of drugs with the two main regimens being oral clindamycin (600 mg every 8 hours) with quinine (650 mg every 8 hours), or atovaquone (750 mg every 12 hours) with azithromycin (500 mg on day 1, then 250 mg/day thereafter). For high-grade parasitemia, quinine /clindamycin combination therapy had been the most evaluated, in era prior to exchange transfusions.[7] Atovaquone and azithromycin were compared with clindamycin and quinine in a prospective, nonblinded, randomized trial of 58 adult patients with non-life-threatening babesiosis.[8] The median level of parasitemia in these patients was only 0.5%. Atovaquone plus azithromycin was found to be better tolerated and equally effective in clearing parasitemia and resolving symptoms compared to the combination of quinine and clindamycin. In immunocompromised patients with babesiosis, successful outcome has been reported using atovaquone combined with higher doses of azithromycin (600-1000 mg per day).[9] Such high dose of azithromycin can cause significant cholestasis, as noted in our patient. Triple-drug therapy ,with addition of doxycycline, has been successful in a case of refractory babesiosis. A severely immunosuppressed HIV-infected patient with chronic babesiosis who did not respond to clindamycin and quinine, improved with clindamycin, doxycycline, and azithromycin, although the infection was not eradicated.[10] For parasitemias >10% causing significant hemolysis, renal, hepatic or pulmonary decompensation, exchange transfusion remains the therapy of choice, in conjunction with antimicrobial agents.[11]

In our patient, parasitemia apparently had cleared by week 4 of therapy with atovaquone, doxycycline and high-dose azithromycin. However, the patient still had significant fatigue and rising antibody titers. Subsequently, the patient was continued on clindamycin, atovaquone and doxycycline until resolution. These 3 drugs in combination

have not been described for use in babesiosis previously.

The mechanisms of drug actions during treatment of babesiosis may explain the applicability of the triple-drug therapy used in our patient. In each of the 2 common regimens, one drug acts as the principal antiparasitic agent, while the second agent facilitates the former. Atovaquone's antibabesial effects involve inhibition of mitochondrial electron transport, but when used alone it is not as effective as in combination therapy, as animal studies showed recrudescence of parasitemia when treated with atovaquone alone, and clearance of the infection with combination therapy using atovaquone and azithromycin.[12] Azithromycin inhibits RNA-dependent protein synthesis at the chain elongation step and binds to the 50S ribosomal subunit resulting in blockage of transpeptidation. Quinine depresses oxygen uptake and carbohydrate metabolism and intercalates into DNA, disrupting the parasite's replication and transcription. Clindamycin reversibly binds to 50S ribosomal subunits preventing peptide bond formation thus inhibiting bacterial protein synthesis. Doxycycline also is an inhibitor of protein synthesis.

Therefore, atovaquone and quinine work at the mitochondrial and nuclear levels in these parasites, while clindamycin and azithromycin potentiate the opsonization and phagocytosis of the Babesia by disrupting babesial protein synthesis. The latter agents cause changes in cell wall surfaces, decrease adherence of the parasite to host cells and facilitate intracellular killing of organisms by the former two agents. This might explain the increased activity of combination therapy using an intracellular antiparasitic agent with one of the protein synthesis inhibitors. ■

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CME Questions

8. Behavioral problems are more common in foreign-born adoptees who:

a. are girls
b. are from mainland China
c. were previously institutionalized
d. were adopted during the first year of life

9. Which of the following statements regarding treatment recommendations for gonorrhea in the United States is correct?

a. Development of fluoroquinolone resistant *N. gonorrhoeae* is confined to the United States.
b. Azithromycin is now recommended as a first choice option in all gonorrhea infections.
c. Fluoroquinolones may still be used to treat uncomplicated gonorrhea infections in heterosexual men.
d. Ceftriaxone, 125 mg IM, is recommended for uncomplicated urogenital and anorectal gonococcal infections.

10. Which of the following statements regarding malaria relapses is accurate:

a. *P. falciparum* and *P. malariae* commonly cause relapses of malaria.
b. *P. vivax* and *P. ovale* produce hypnozoites that may cause malaria relapses.
c. *P. vivax* parasites that cause initial malaria episode usually have the same genotype as those that cause relapses.
d. Hypnozoites usually remain dormant in red blood cells after they enter the erythrocytic stage.

Answers: 8.c 9.d 10.b

CME Objectives

• To present the latest data regarding the diagnosis and treatment of various travel-related diseases;
• To present new data concerning recommended precautions and prophylaxis for patients traveling to specific areas of the world; and
• To alert the readers to recent disease outbreaks and epidemics. ■

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.

Risk With Preventative Antibiotics Outweighs Benefit for Most

Sweeping new changes have been made to the guidelines for prevention of endocarditis in patients undergoing dental procedures. The new recommendations dramatically reduce the indications for dental prophylaxis and reduce the number of patients who need preprocedure antibiotics. The guideline was issued by the American Heart Association in conjunction with the American Dental Association, Infectious Diseases Society of America, and the Pediatric Infectious Diseases Society and was published online April 19, 2007, in *Circulation*. The guidelines reflect evidence that the risk of taking preventative antibiotics outweighs the benefit for most patients. It is also been found that infectious endocarditis (IE) is more likely to result from frequent exposure to random bacteremias from activity such as flossing and brushing than from dental work. Specifically, the guidelines say that prophylactic antibiotics are no longer required for patients with mitral valve prolapse, rheumatic heart disease, bicuspid valve disease, calcified aortic stenosis, or congenital heart conditions such as ventricular septal defect, atrial septal defect, and hypertrophic cardiomyopathy. There are still patients who are at extremely high risk of IE who should continue to receive prophylactic antibiotics: patients with artificial heart valves, a history of infective endocarditis, congenital heart disease including unrepaired or incompletely repaired cyanotic congenital heart disease, including those with palliative shunts and conduits, those with a completely repaired congenital heart defect with prosthetic material during the first 6 months after the procedure, repaired congenital heart defect with residual defect at the site or adjacent to the site of a prosthetic patch or prosthetic device, or a cardiac transplant patient with a cardiac valvulopathy. Antibiotic prophylaxis is no longer recommended for any other form of congenital heart disease. Dosing regimens are essentially the same as previous recommendations and include oral amoxicillin 2 gm 30 to 60 minutes prior to procedure. Oral alternatives include cephalexin, clindamycin, azithromycin or clarithromycin. Parenteral regimens include ampicillin, cefazolin, ceftriaxone, and clindamycin. The guideline also no longer recommends antibiotics to prevent IE in patients undergoing genitourinary or gastrointestinal tract procedures (*Circulation* 2007, doi:10.1161/CIRCULATIONAHA.106.183095). The full guideline is available at http://www.ada.org/prof/resources/ topics/infective_endocarditis_guidelines.pdf. ■

Gonococcal Infections, CDC's Updated Treatment

The CDC has issued updated treatment recommendations for gonococcal infections and associated conditions due to the high level of resistance of gonorrhea to fluoroquinolones. The agencies Gonococcal Isolate Surveillance Project demonstrates that fluoroquinolone-resistant gonorrhea is continuing to spread and is now widespread

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throughout United States. Therefore, fluoroquinolones such as ciprofloxacin, ofloxacin, or levofloxacin are no longer recommended. Current recommended regimens for gonococcal infections of the cervix, urethra, and rectum are ceftriaxone 125 mg IM and a single dose or cefixime 400 mg orally in a single dose plus treatment for chlamydia if chlamydial infection is not ruled out. Uncomplicated gonococcal infections of the pharynx should be treated with ceftriaxone 125 mg IM plus treatment for chlamydia, if chlamydial infection is not ruled out. Disseminated gonococcal infection should be treated with ceftriaxone 1 g IM or IV every 24 hours. Pelvic inflammatory disease may be treated with parenteral and oral therapy. Parenteral therapy regimens include cefotetan or cefoxitin plus doxycycline or clindamycin plus gentamicin. An alternative regimen is ampicillin/sulbactam plus oral doxycycline. Oral therapy can be considered in women with mild to moderate disease. With the loss of fluoroquinolones, cephalosporins are the mainstay of most regimens. For patients who are highly allergic to cephalosporins, spectinomycin may be considered although it is not generally available in this country. Another option is azithromycin, however, prescribing should be done in consultation with an infectious disease specialist due to concerns over emerging antimicrobial resistance to macrolides. The CDC's full recommendations are available online at www.cdc.gov/std/treatment/2006/updated-regimens.htm. ■

Head Lice — Malathion First-Line Treatment

Malathion should be first-line treatment for children who have lice according to a new review in the journal *Pediatrics*. Head lice have become resistant to nearly all first-line treatments in United States including permethrin, which has been considered first-line treatment for years. Malathion, in the formulation containing isopropyl alcohol and terpineol, is safe and effective for lice and all existing points within the life cycle, and generally requires a single treatment, reducing the duration of infestation, and lost time from school and work. Concern about flammability seems to be over emphasized, as there have been no reported cases of bodily injury related to burns (*Pediatrics* 2007. 119:965-974).

Statins, May Cut the Risk of Cataracts

Statins, the cholesterol wonder drugs, have been associated with a number of other benefits including reduction of inflammation within the arteries, improved bone density, reduction in the risk of colon cancer, renoprotective effects, and reduction in the risk of Alzheimer's disease and other dementias. Now, a new study suggests that the drugs may also cut the risk of cataracts by 50%. Researchers from Australia reviewed the rate of cataract development in 3,654 elderly patients. After 10 years, after controlling for age, gender and others factors, the hazard ratio for any type of cataract in statin users was 0.52. In subgroups, there was a decreased risk of nuclear cataracts (HR = 0.66) and cortical cataracts (HR =0.76), but neither of these reached statistical significance. The authors conclude that there may be a protective influence of statins on cataracts and this needs to be further explored (*Am J Ophthalmol* 2007; 143:687-689). ■

FDA Actions

Sanofi Aventis has been approved to produce a vaccine to prevent bird flu in humans. The vaccine against the H5N1 virus will not be produced commercially, but will instead be stockpiled by the U.S. government for distribution in case of the outbreak. The FDA admits that the vaccine is not optimal, requiring a higher dose than normal flu vaccine, and 2 shots which must be given 28 days apart. But until other vaccines are developed, this vaccine will be used as the "interim measure."

The FDA is recommending updating black box warning regarding suicidality in young adults (under age 24) starting on antidepressants, calling for appropriate monitoring and close observation. The new recommendation should also include the statement that there was no increase in suicidality in adults over the age of 24, and a decrease in the risk in adults over the age of 64.

The FDA has approved generic versions of 2 of the most popular drugs of the last decade, Ambien (zolpidem) and Zoloft (sertraline). Zolpidem will be available in 5 mg and 10 mg immediate-release tablets. Thirteen manufactures have received approval to market the product. Sertraline is approved in the 25 mg, 50 mg and 100 mg strengths, and will be produced by Ranbaxy Laboratories.

The FDA has issued a warning about the health risks of dietary supplements touted as sexual enhancement products and treatments for erectile dysfunction that have been distributed under the trade names True Man and Energy Max. Both drugs have been sold throughout United States. Energy Max was found to contain an analogue of sildenafil, the active ingredient in Viagra, while True Man was found to contain an analogue of sildenafil and vardenafil, the active ingredient in Levitra. Both drugs can have serious interactions with nitrates. ■