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INSIDE

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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. 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, reports no financial relationship relevant to this field of study.

Oral Antibiotics for Pyelonephritis in Children

ABSTRACT & COMMENTARY

By Hal B. Jenson, MD, FAAP

Chief Academic Officer, Baystate Health Professor of Pediatrics and Dean of the Western Campus of Tufts University School of Medicine

Dr. Jenson is on the speaker's bureau for Merck.

Synopsis: Treatment of the first episode of pyelonephritis in children with oral antibiotics alone for 10 days is not inferior to parenteral therapy for 3 days followed by oral therapy for 7 days.

Source: Montini G, et al. Antibiotic treatment for pyelonephritis in children: Multicentre randomised controlled non-inferiority trial. *BMJ* 2007 July 4 (Epub ahead of print).

A MULTICENTER NON-INFERIORITY OPEN-LABELED RANDOMized controlled trial of oral amoxicillin-clavulanate (50 mg/kg/day divided 3 times a day for 10 days) compared to initial parenteral treatment with ceftriaxone (50 mg/kg/day as a single daily dose for 3 days) followed by oral amoxicillin-clavulanate (for 7 days) for children < 6 years of age with acute pyelonephritis and no anatomic urogenital tract abnormalities was conducted from 2000 to 2004 among 502 children 1 month to 7 years of age in 28 primary care practices in northern Italy. *Escherichia coli* was the pathogen in 436/462 (94.4%) of urine cultures. Antimicrobial resistance was 25/407 (6%) to amoxicillin-clavulanate and 3/343 (<1%) to ceftriaxone. Ultrasonography and DMSA scintigraphy were planned no later than 10 days after initiation of antibiotic treatment. The primary outcome measurement was renal scarring at 12 months, which was similar for both oral treatment only (27/197 [13.7%]) vs initial parenteral treatment (36/203 [17.7%]), risk difference -4% (95% CI, 11.1% to 3.1%). Renal scarring was also similar among the 278 children with pyelonephritis that was confirmed by DMSA scintigraphy (26/96 [27.8%] vs 33/100 [33%]). There were no significant differences between the 2 groups for secondary outcomes of: time to defervescence (36.9 hours [SD

19.7 hours] vs 34.3 hours [SD 20 hours], mean difference 2.6 hours [0.9 to 6.0 hours]); white cell count ($9.8x10^9$/L [SD 3.5 $x10^9$/L] vs $9.5x10^9$/L [SD $3.1x10^9$/L], mean difference $0.3x10^9$/L [0.3 to $0.9x10^9$/L]); and sterile urine after 3 days (185/186 vs 203/204, risk difference 0.05% [95% CI, 1.5% to 1.4%]). One patient in each group had a positive urine culture after 3 days; each had *E. coli* cultured initially and *Pseudomonas aeruginosa* cultured on the second urine sample. The duration of hospitalization was similar in both groups (5.17 days vs 5.05 days); by study design all children were hospitalized for a minimum of 3 days.

COMMENTARY

Acute pyelonephritis in young children is a serious concern because of the risk for sepsis, and especially the risk of sequelae of renal scarring, which is thought to be partially preventable by prompt, adequate treatment of acute infections. The recommendations for initial treatment of uncomplicated first urinary tract infections include broad guidelines that permit both parenteral and oral regimens according to the judgment of the physician. Pediatricians have traditionally considered pyelonephritis, or upper tract infection, as more serious and requiring initial parenteral therapy, while oral therapy is considered sufficient for cystitis, or lower tract disease. However, there are no reliable, routinely available methods to clinically distinguish between upper and lower tract infections and pediatricians frequently presume the presence of upper tract disease and initiate parenteral therapy.

Numerous studies of various parenteral antibiotic regimens have shown effectiveness for treatment of urinary tract infections in children. Only 1 previous study, among children < 2 years of age, compared exclusive oral treatment with initial parenteral antibiotics, and showed no difference in renal scarring (9.8% of children treated orally vs 7.2% of children treated intravenously; mean extent of scarring of approximately 8% in both groups) between the 2 groups at 6 months. This new study shows that the first urinary tract infection in children < 6 years of age without urogenital tract abnormalities may be effectively treated with an exclusive regimen of oral amoxicillin-clavulanate for 10 days. This has the obvious advantages of ease of administration and also, as outpatient therapy, the potential to reduce healthcare costs without adversely affecting outcome. Adherence to an oral antibiotic regimen at home is critical. ■

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Prophylaxis for Recurrent UT Infections in Children

ABSTRACT & COMMENTARY

By Hal B. Jenson, MD, FAAP

Synopsis: A large primary care pediatric study of recurrent urinary tract infections found a 12% per year recurrence rate with risk factors being white race, age 3-5 years, and grade 4-5 vesicoureteral reflux. Antimicrobial prophylaxis did not reduce the risk for recurrence but was associated with increased risk of recurrent infection caused by resistant organisms.

Source: Conway PH, et al. Recurrent urinary tract infections in children. Risk factors and association with prophylactic antibiotics. *JAMA* 2007;298:179-186.

From a network of 27 primary care practices with 74,974 children in urban, suburban, and semi-rural settings in 3 states during 2001-2006, 666 children < 6 year of age who were otherwise healthy had a urinary tract infection (UTI), for a first-UTI incidence rate of 0.007 per person-year. Of these children, 611 were evaluable, most were female (543 [88.9%]) and 83 (13.6%; 0.12 per person-year after the first UTI) had a recurrent UTI. A nested case-control analysis of

these 83 children showed that the risk factors for recurrence of UTI were white race (0.17 per person-year; hazard ratio [HR] 1.97; 95% confidence interval [CI], 1.22-3.16), age 4-5 years (0.22 per person-year; HR 2.47; 95% CI, 1.19-5.12), and grade 4-5 vesicoureteral reflux (0.60 per person-year; HR 4.38; 95% CI, 1.26-15.29). Sex and grade 1-3 vesicoureteral reflux were not associated with risk of recurrence. Race was considered as white vs non-white because < 3% of children were Asian and there were no Native American children, and ethnicity was not analyzed separately because < 3% of the children were Hispanic. Most children did not have a voiding cystourethrogram (VCUG; 400 [65.5%]) and did not receive antimicrobial prophylaxis (483 [79.1%]). Prophylactic antimicrobials that were prescribed included trimethoprim-sulfamethoxazole (61%), amoxicillin (29%), nitrofurantoin (7%), or other antimicrobials (3%). Resistant organisms including *Escherichia coli* (78%), other gram-negative bacilli (16%), Enterococcus (4%), and other organisms (2%) were cultured from 51 (61%) of the 83 recurrent cases. Antimicrobial prophylaxis was not associated with decreased risk of recurrent UTI but was associated with an increased risk of infections caused by resistant organisms, from 53.1% to 89.5% (odds ratio, 7.5;95% CI, 1.60 35.17).

COMMENTARY

Urinary tract infection is a frequent diagnosis among young children. This large study showed a cumulative incidence of UTI among children in the first 6 years of life of 4.2%. Recurrence is a significant concern, and in this study the recurrence rate for children < 6 years of age following diagnosis of a first UTI was 12% per year. This recurrence rate is lower than the rates previously reported in other studies from referral populations.

The optimal management of urinary tract infections in children is shaped largely by consensus opinion because of the paucity of high-quality controlled trials. The 1999 American Academy of Pediatrics practice guideline for UTI (American Academy of Pediatrics: Practice parameter: The diagnosis, treatment, and evaluation of the initial urinary tract infection in febrile infants and young children. *Pediatrics* 1999;103:843-852.) recommends an imaging study after a first UTI for children < 2 years of age to evaluate for vesicoureteral reflux, which is present in about one-third of children with UTI and theoretically increases the risk for recurrent UTI and subsequent renal scarring. If reflux is present, daily antimicrobial prophylaxis is usually recommended to prevent recurrent UTI. This new study showed no association between antimicrobial prophylaxis and risk for recurrent UTI, and a > 7-fold risk of recurrent infection caused by resistant organisms. Given these findings, and other recent randomized controlled pediatric trials of antimicrobial prophylaxis that showed no reduction in the risk of UTI recurrence or renal scarring, there may be no specific benefit of prescribing antimicrobial prophylaxis following an uncomplicated first UTI in young children. It may complicate treatment of recurrent UTI because of selection for resistant organisms. Regardless of the administration of prophylactic antibiotics, close follow-up is essential and may be preferred as the core of the management strategy by many physicians and families for children without urogenital tract abnormalities following a first UTI. ■

Pediatric Malignancies Masquerading as Infections

ABSTRACT & COMMENTARY

By Hal B. Jenson, MD, FAAP

Synopsis: Review of initial infectious disease consultations for children with malignancy showed that prolonged fatigue, bone pain, hepatomegaly, splenomegaly, hematologic abnormalities, or elevated LDH may be the revealing sign of pediatric malignancy.

Source: Forgie SE, Robinson, JL. Pediatric malignancies presenting as a possible infectious disease. *BMC Infectious Diseases* 2007;7:44 (available at www.biomedcentral.com/1471-2334/7/44).

Among 561 patients diagnosed with malignancy from 1993-2003 in the Northern Alberta Children's Cancer Program, infectious diseases consultation was initially requested for 21 children (<15 years of age) a median of 7 days (range, 0-32 days) prior to definitive diagnosis. The reasons for consultation included suspected musculoskeletal infection (9), fever (4), possible respiratory tract infection (2), possible soft tissue infection (2), splenomegaly and lymphadenopathy (1), leukocytosis (2), and possible neurocysticercosis (1). The patients reported symptoms of fever (15), weight loss of up to 10 kg (7), bone pain (6), fatigue from 1-70 days duration (6), and headache (6). Findings on physical examination included hepatomegaly (4), palpable splenomegaly (8), and a wide variety of rashes

(7). Imaging studies revealed hepatomegaly in 2 additional patients and splenomegaly in 3 additional patients. All but 2 patients had an abnormal hemoglobin, white blood cell count, and/or platelet count. Malignancy was considered as probable in the differential diagnosis by both the referring physician and the consultant in 9 cases, and by either the referring physician or the consultant in 9 cases. Malignancy was not considered by either in 1 case of leukemia that was initially diagnosed as suppurative arthritis, and the 2 cases of possible soft tissue infection, which were a fibrous histiocytoma and a rhabdomyosarcoma. Three patients had both infection and malignancy on initial presentation. The types of malignancy included leukemia (13), lymphoma (3), rhabdomyosarcoma (1), Langerhans cell histiocytosis (1), fibrous histiocytosis (1), ependymoma (1), and neuroblastoma (1). Only 2 patients (10%) had a normal hematologic finding on complete blood count, and 10 patients (48%) had elevated lactate dehydrogenase (LDH). Delay in diagnosis that was directly attributable to investigation or therapy for infection occurred in only 2 patients: one patient was treated for suppurative arthritis for 11 days with leukopenia attributed to antibiotics, and one patient was diagnosed with discitis with an MRI scheduled as an outpatient 8 days later. Both patients had abnormalities on complete blood counts.

COMMENTARY

Malignancy, infection, and collagen vascular diseases are the most common causes of fever of unknown origin among children and are the primary diagnostic considerations for children with ambiguous presentations such as constitutional symptoms and non-specific findings. This study confirms that delayed treatment for pediatric malignancies because of misdiagnosis of an infectious disease is rare.

There are several clinical caveats from this report. Bone pain, which was present in about one-third of these children, is common in leukemia and malignancy, which should be considered along with infection for all children with vague musculoskeletal symptoms. Abdominal imaging for hepatomegaly and splenomegaly was an important diagnostic tool, and when positive with an uncertain diagnosis suggests malignancy. Abnormal results of the complete blood count were present in 90% of patients, and physicians should be cautious in attributing these abnormalities to non-malignant processes. An elevated LDH, indicative of rapid cell turnover in malignancy and cell damage in other processes, was present in about half of patients. In summary, prolonged fatigue, bone pain, hepatomegaly, splenomegaly, hematologic abnormalities, or elevated LDH, even when only one of these is present, suggest malignancy even when the consultation is requested because of a possible infectious disease. ■

Rapid Diagnostic Testing for Malaria — It's Finally Here!

SPECIAL REPORT

By Stan Deresinski, MD

Source: CDC. Notice to readers: malaria rapid diagnostic test. *MMWR* 2007;56(27):686.

Synopsis: The BinaxNOW® Malaria test, a 15 minute immunochromatographic test with a high sensitivity for the diagnosis of malaria due to Plasmodium falciparum *has been approved for use in the FDA.*

The diagnosis and treatment of severe forms of malaria is an emergent matter. However, the microscopic diagnosis of malaria requires skill and experience and the availability of capable personnel at all hours of the day and night is becoming increasingly problematic in U.S. hospitals. A number of effective rapid diagnostic tests (RDT) not requiring the skill of the microscopist have been available in many places of the world, but not in the U.S., for several years. As a result, despite the need for immediate examination of thick and thin blood smears, in some facilities the smears are saved until a qualified individual is available to examine them, or they are sent to outside laboratories. This approach, as well as misdiagnosis, may lead to fatal delays in initiation of therapy for severe malaria due to *Plasmodium falciparum*.

However, on June 13, 2007, the FDA approved the first malaria RDT authorized for use by laboratories in the U.S., the BinaxNOW® Malaria test (Inverness Medical Professional Diagnostics, Scarborough, Maine). This immunochromatographic test uses whole blood and takes approximately 15 minutes to complete. It targets 2 antigens, one specific to *P. falciparum* (histidine-rich protein 2 or HRP2) and one found in all 4 human plasmodial parasites (an aldolase).[1] Thus, while it specifically identifies *P. falciparum*, it cannot distinguish among the other species. It is recommended that laboratories using BinaxNOW should have available to them blood containing *P. falciparum* to serve as a positive control.

Because of their infrequency in trials evaluating the

test, available data are inadequate to confidently assess the ability of BinaxNOW to detect cases of infection with either *Plasmodium ovale* or *Plasmodium malariae*. Furthermore, it is unable to detect the presence of a second malarial species in patients with mixed infection that include *P. falciparum*. Finally, it may miss cases of infection with low-level parasitemia. For these reasons, microscopy should be performed in conjunction with the RDT. In cases of a positive RDT test, microscopy allows for confirmation of infection, speciation of non-*falciparum* parasites, and detection of mixed infection, as well as determination of parasite density. Microscopy may also be considered in patients with a negative test but with a high pre-test probability of infection. This may be especially useful if infection with *P. ovale* or *P. malariae* are suspected. Finally, serial microscopy must be used to determine changes in the degree of parasitemia in response to therapy.

The sensitivity and specificity of the test in the diagnosis of *P. falciparum* infection in Thailand in a cohort with a prevalence of malaria by microscopy was 13% were 100% and 96.2%, respectively.[2] The sensitivity for diagnosis of *P. vivax* infection was 87.3% and the specificity for non-*falciparum* infections was 100%. In a study in returned travelers in an area not endemic for malaria, the sensitivity and specificity relative to microscopic diagnosis were 98.8% and 98.4%, respectively.[3] In another study in returned travelers in which it was compared to diagnosis by PCR, the BinaxNOW test had a sensitivity of 94%-96% in the diagnosis of *P. falciparum* infection and 84% for non-*falciparum* infections.[4] The overall specificity was 99%. False negatives have been associated with low levels of parasitemia and false positives may occur in the presence of rheumatoid factor. ■

References:

1. Moody A. Rapid diagnostic tests for malaria parasites. *Clin Microbiol Rev* 2002;66-78.
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3. De Monbrison F, et al. Comparative diagnostic performance of two commercial rapid tests for malaria in a non-endemic area. *Eur J Clin Microbiol Infect Dis* 2004; 23:784-786.
4. Farcas GA, et al. Evaluation of the Binax NOW ICT test versus polymerase chain reaction and microscopy for the detection of malaria in returned travelers. *Am J Trop Med Hyg* 2003; 69:589-592.

Zika in Yap

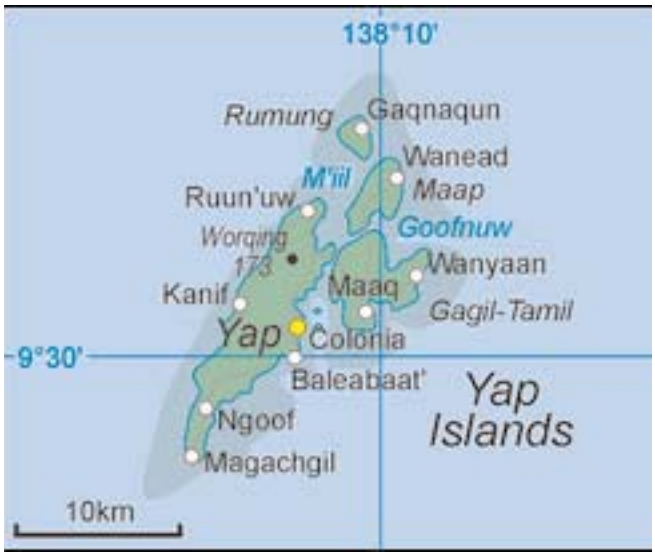
SPECIAL REPORT

By Stan Deresinski, MD

Source: www.cdc.gov/news/2007/06/zika_yapislands.html

Synopsis: An outbreak of mild dengue-like illness on the Pacific island of Yap was due to a flavivirus, the Zika virus.

An outbreak of dengue-like illness that began in May, 2007, on Yap, one of the Carolina islands of the Federated States of Micronesia, proved to be due to Zika virus. As of early August, 99 confirmed and 54 probable cases had been identified, with the most recent case dating from July 17th. Additional probable cases have been seen on neighboring islands. The cause of the outbreak was determined by the Arbovirus Diagnostic Laboratory of the CDC.



*The Yap Islands, or Yap, composed of 4 continental islands located in the Caroline Islands of the Federated States of Indonesia in the western Pacific Ocean. (*Image by Aotearoa from Poland, GNU FDL from www.cdc.gov/news/2007/06/zika_yapislands.html).

Dengue is a mosquito-borne flavivirus first identified in 1947 in a sentinel rhesus monkey stationed on a tree platform in the Zika forest, near Entebbe, Uganda and monkeys are presumed to be the natural reservoir of the virus. Symptoms and signs are generally relatively mild and consist of fever, conjunctivitis, arthralgias, and maculopapular rash. The illness lasts 2 to 7 days. Treatment is symptomatic. Serosurveys indicate that Zika virus infections occur in Africa, Southeast Asia, and Malaysia.

For instance, a seroprevalence study found an incidence of 31% in several communities in the Nigerian state of Oyo between 1971 and 1975.[1] In addition, an outbreak occurred in Indonesia almost 3 decades ago.

With the assistance of 2 Epidemiologic Service Officers of the CDC, control measures are aimed at reducing peridomestic mosquito breeding sites in open water containers, aerial spraying, and personal protective measures aimed at prevention of mosquito bites.[2] ■

References:
1. Fagbami AH. Zika virus infections in Nigeria: virological and seroepidemiological investigations in Oyo State. *J Hyg* 1979; 83:213-219.
2. http://www.cdc.gov/news/2007/06/zika_yapislands.html

Q Fever in U.S. Soldiers Deployed to Iraq

ABSTRACT & COMMENTARY

By Dean L. Winslow, MD, FACP, FIDSA

Chief, Division of AIDS Medicine, Santa Clara Valley Medical Center; Clinical Professor of Medicine, Stanford University School of Medicine

Dr. Winslow serves as a consultant to Siemens Diagnostics and is on the Speakers Bureaus of Boehringer-Ingelheim and GSK.

Synopsis: Three soldiers who were recently or currently deployed to Iraq are described. All presented with various combinations of fever, abdominal pain, pneumonia, and liver function abnormalities. Two had clinical and radiographic evidence of acalculous cholecystitis. Treatment with doxycycline may shorten the duration of symptoms and prevent chronic disease.

Source: Hartzell JD, et al. Atypical Q Fever in US Soldiers. *CDC Emerg Infect Dis*. 2007 Aug. Available from www.cdc.gov/EID/content/13/8/1247.htm

THIS INTERESTING REPORT WRITTEN BY AN ID Fellow at Walter Reed Army Medical Center (WRAMC) describes 3 cases of Q fever in deployed (or recently redeployed) soldiers serving in Iraq.

The first patient was a 22-year-old male Army National Guard member who presented to a New Hampshire ER 7 days after returning from Iraq with flu-like symptoms, fever, leukopenia, a normal chest X-ray and modestly elevated serum transaminases. He was empirically treated with azithromycin and ceftriaxone. While his fever decreased he developed abdominal pain, dyspnea, and worsening transaminases with his ALT reaching 993 U/L and alkaline phosphatase 269 U/L. After transfer to WRAMC chest and abdominal CT scans showed bilateral ground glass pulmonary infitrates and gallbladder wall thickening without evidence of ductal dilatation. He was treated with doxycycline and his signs and symptoms resolved. Diagnosis of Q fever was made serologically by demonstrating both IgM antibodies to Coxiella burnettii present at 1: 256 and IgG antibodies at 1:128 in convalescent sera and negative antibodies in acute sera.

The second patient was 24-year-old male Army National Guard soldier who was admitted to the 28th Combat Support Hospital (CSH) in Baghdad with flu-like symptoms, nausea and a dry cough. He was febrile to 40.2 deg C. Mild epigastric tenderness was present and the patient had mild leukopenia, platelets 130,000, and markedly elevated ALT and AST (approx. 800 U/L for both). Abdominal CT scan showed gallbladder wall thickening and enhancement. Q fever was considered in the differential diagnosis and the patient received doxycycline and metronidazole. His fever decreased, metronidazole was discontinued but doxycycline was continued for a 14-day course and he was transferred to Landstuhl Regional Medical Center (LRMC). Serologic studies demonstrated high titer IgM antibodies to *C. burnetii* (1:2048) in both acute and convalescent phase sera. He made a complete recovery and was returned to duty.

The last patient was a 34-year-old female active duty soldier with a history of asthma who presented to one of the Baghdad area Troop Medical Clinics with flu-like symptoms. She was initially treated symptomatically but returned with altered mental status, dyspnea and abdominal pain. Chest CT scan showed a left lower lobe infiltrate. Abdominal ultrasound was normal. She was transferred to the 10th CSH in Baghdad. She remained febrile to 39.8 deg C and was tachycardic. Mild increases in serum transaminases were observed. She was treated with levofloxacin but respiratory failure requiring intubation and mechanical ventilation developed. She was evacuated initially to LRMC where bronchoscopy was performed. Follow up chest X-rays showed evidence of ARDS. Doxycycline was given and the patient was transferred to WRAMC. By the time she arrived in Washington, DC, she was afebrile and her respiratory status rapidly improved and she was extubated. She completed a 14-day course of doxycycline and recovered completely.

■ COMMENTARY

Acute Q fever often presents with fever, pneumonia, and/or hepatitis but other manifestations can include

meningoencephalitis and myopericarditis.[1,2] Chronic infection may manifest as culture-negative endocarditis. Only about 12 cases of acute cholecystitis due to Q fever have been described.[3] Interestingly, none of the 3 soldiers described in this paper reported typical zoonotic exposures.

This series of patients reminds us of the protean manifestations of Q fever and of the importance of including Q fever in the differential diagnosis of fever, pneumonia, and hepatitis in soldiers deployed (or recently returned from deployment) to Southwest Asia. Doxycycline remains the antimicrobial of choice for this infection and likely shortens the duration of acute illness and prevents chronic disease (endocarditis) from developing. ■

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1. Parker NR, et al. Q fever. *Lancet* 2006;367:679-688.
2. Raoult D, et al. Q fever 1985-1998: clinical and epidemiological features of 1,383 infections. *Medicine* 2000;79:109-123.
3. Reina-Serrano S, et al. Q fever-related cholecystitis: a missed entity? *Lancet Infect Dis* 2005;5:734-735.

West Nile Virus Neutralization by Plasma Immunoglobulin

ABSTRACT & COMMENTARY

By Joseph F. John, Jr., MD, FACP, FIDSA, FSHEA

Associate Chief of Staff for Education, Ralph H. Johnson Veterans Administration Medical Center; Professor of Medicine, Medical University of South Carolina, Charleston, SC.

Dr. John is a consultant for Cubist, Genzyme, and bioMerieux and is on the speaker's bureau for Cubist, GSK, Merck, Bayer, and Wyeth.

Source: Planitzer CB, et al. West Nile Virus neutralization by US plasma-derived immunoglobulin products. *J Infect Dis* 2007;196:435-440.

THERE IS NO PROVEN THERAPY FOR INFECTION DUE TO the mosquito-borne flavivirus West Nile Virus, introduced to a fully susceptible U.S. population in 1999. There have been more than 2 million cases since its introduction and the spectrum of disease has expanded to include diverse neurological manifestations. Nevertheless, most infection due to WNV is asymptomatic so it is anticipated that, with time, that an increasing proportion of the American population will have been infected.

Most of the plasma distributed globally as fractionated products (including immunoglobulin) comes from the United Staes. So, with an ever-increasing proportion of the U.S. population exposed to WNV, we would expect a higher rate of neutralizing antibody to WNV in U.S. immunoglobulin lots compared, for example, to European-derived immunoglobulin.

Workers at Baxter BioScience in Vienna, Austria, sought to 1) determine if the concentration of WNV neutralizing antibody in U.S. vs European immunoglobulin lots and 2) determine the potential for WNV antibody in commercial preparations of immunoglobulin would be protective in a WNV animal model.

Planitzer et al used a WNV isolated from a snowy owl to determine neutralizing antibody titres against an inoculum of 10,000 TCID50 for various immunoglobulin lots from Europe and the United States. Female BALB/c mice infected with WNV were treated subcutaneously with either U.S. or European immunoglobulin, neutralizing titers of 2.4 or 0.1 respectively.

Results of these experiments showed that U.S.-sourced products averaged titers of 1.4 but they ranged from 0.3 to 2.9. The reason for this broad range emerged when state-by-state incidence analyses were performed. The states with > 5 cases per 100,000 were Nebraska, South Dakota, North Dakota, Wyoming, Colorado, and Idaho. Almost no cases from the Eastern United States emerged from these state-specific analyses.

Using a mouse model and a sc challenge of 100,000 TCID50, only 10% of mice would be expected to survive. When mice were treated with the U.S.-derived product (Gammagard Liquid/KIOVIG with a neutralization titre of 2.4) 90% of mice survived as compared to only 20% of mice treated with the European-derived product and to 10% survival in controls. ($P < 0.001$ vs control).

COMMENTARY

The major findings of this study supported by Baxter BioScience was that U.S.-based immunoglobulin had substantial titers of WNV neutralizing antibody and that immunoglobulin protected WNV-infected mice. To make a leap of faith and apply these findings by treating WNV-infected patients with immunoglobulin may at first glance seem reasonable.

The 2 reports suggesting that immunoglobulin may be effective at treating WNV (those quoted by the authors) are more than several years old [*J Infect Dis* 2003;188:1-4; *Emerg Infect Dis* 2001;7:759]. Clinical trials are now underway to evaluate more thoroughly the efficacy of Omr-IgG-am in patients with or at high risk for WNV disease (http://clinicaltrials.gov/show/NCT00069316).

If physicians choose to use commercial U.S.-derived immunoglobulin to treat WNV-infected patients, they would like to assume the highest possible titre of anti-WNV antibody in these preparations. Further geographic seroanalysis is necessary to verify the findings of this report that some states have significantly higher titres. Moreover, it would be very helpful if Baxter BioScience itself could provide some real-time information to prescribers about the neutralization capacity of immunoglobulin lots available for use. The authors touch on this idea but stop short of suggesting that the company could provide a rapid response as a clinical service. If such a rapid response is not economically feasible, perhaps those lots distributed for use could be designated of high, medium, or low anti-WNV antibody.

Of course, any empirical therapy with IVIG should not include European lots since, as shown in this study, those lots have neither adequate neutralization titres nor are they protective in the mouse WNV. As WNV spreads, as this summer's trends suggest, there may be value in WNV serological testing of immunosuppressed patients. Substitution therapy with IVIG for immunodeficient individuals would ideally be done with lots with good neutralization levels.

West Nile Virus is a relatively new virus for North American populations. Our strategies for prevention, prophylaxis and therapy of WNV are evolving with the virus. Creative discoveries like the one by Planitzer et al will be needed to deal more effectively with disease due to WNV, particularly when it presents in its more severe forms. ■

Rabies Symposium at CISTM

SPECIAL REPORT

By Lin Chen, MD

Assistant Clinical Professor, Harvard Medical School; Director Travel Resource Center, Mount Auburn Hospital, Cambridge, MA

Dr. Lin H. Chen reports no financial relationship relevant to this field of study. This article originally appeared in the August issue of Travel Medicine Advisor. *It was edited by Frank Bia, MD, MPH, who received funds from Johnson & Johnson, and peer reviewed by Philip Fischer, MD, DTM&H, who reports no financial relationships relevant to this field of study.*

The rabies symposium at the conference of the International Society of Travel Medicine in Vancouver, Canada, featured Drs. David Warrell, David Shlim, and Kanitta Suvansrinon. Professor Warrell presented Rabies Update: Epidemiology and Risk including Host Range. He described a 26-year-old woman from the United Kingdom who traveled to Himachal Pradesh, India, where she was bitten by a dog. The wound was cleaned with whisky and the patient treated with antibiotics and homeopathy. One month later, she returned to the UK still needing dressing changes. Two months later, she became tired, had back pain, and was described as "catching her breath when drinking liquids or felt wind." Two days later she experienced cardiac arrest and died 36 hours later.

The annual human deaths from rabies are ~24,000 in India, 3,200 in China, < 40 in North America, 36 in South America, 9 in Russia. In India during 2005, most bites were due to dogs; there were 16 million bites, 20,000 deaths, and 4 million courses of post exposure rabies prophylaxis given. In China for the year 2006, there were 3293 deaths (27% increase from 2005), and 8 million courses post-exposure prophylaxis administered. Rabies was the leading cause of infectious diseases from May 2006 to March 2007. About 95% of bites were from dogs, whose population ranges from 80-150 million. In rural China, 70% of households have guard dogs or pet dogs; only 2% are vaccinated, and usually they are not leashed. There are also many feral dogs. Use of post-exposure prophylaxis is inadequate in rural China. Among 178 rabies victims in Guizhou Province, 66% had no wound treatment, 72% received no vaccine, 28% received too few doses or delayed vaccination, and 99% had no rabies immune globulin (RIG).

Regarding the epidemiology of rabies, the UK had been free of indigenous rabies since 1902. However, in 1996 European bat lyssavirus (EBLV-2a)-infected Daubenton's bats (*Myotis daubentonii*) were discovered. In South Africa, rabies carriers include dog (southeast), fox (west), kudu (north), mongoose (central). In the Middle East, camels are common carriers. In the United States, carriers include skunks and raccoons, as well as bats. In Latin America, vampire bats are common rabies carriers. Less than 500 human deaths have occurred since 1975; children are bitten more commonly on their ears, while adults are bitten on their toes.

In Puerto Maldonado, Peru, bats are present in caves. Between July 2006 and February 2007, 527 people had bites. In arid coastal Peru, irrigation tunnels house vampire bats. Local bat control uses an anticoagulant that is lethal for bats. In Melbourne, flying foxes are of concern. In 1996 and 1998, 2 females died of rabies-like illnesses. The usual perception of rabies is the "mad dog" form but a paralytic type of rabies is also very dangerous.

Rabies transmission can occur through bites, scratches, inhalation, transplanted cornea (1979-1996: 8 recipients in 6 countries), organ transplants (2004: 4 recipients died after receiving transplants of liver, kidneys, iliac artery; more than 1000 contacts were traced, and 20%

did get post-exposure prophylaxis). A study found that among 1,882 foreigners living in Thailand, 1.3% had dig bites, and 8.9% had dog licks. [1]

Rabies is uncontrolled in most countries, and some countries have experienced a recent increase in incidence. It is important to educate travelers, advise that they clean bite wounds immediately and seek effective western post-exposure prophylaxis. Following bites, victims should receive rabies vaccine and rabies immune globulin (RIG). However, the latter may be unavailable or unreliable. Therefore, consider pre-exposure prophylaxis in consideration of time and peace of mind. Pre-exposure prophylaxis has never failed, when boosted after exposure. Intradermal route is an economic solution in some countries, and it is well worth interrupting a trip to get complete post-exposure prophylaxis.

Dr. Shlim discussed pre-exposure rabies immunization for travelers, and highlighted the unique nature of rabies: 1) the time and source of exposure is almost always known and almost always preventable; 2) it is the most lethal infection of humans; 3) it has 100% fatality when encephalitis develops. He addressed the benefits of pre-exposure prophylaxis, what is adequate pre exposure prophylaxis, and when boosters should begin.

What are benefits of pre-exposure prophylaxis?

• Omits need for human rabies immune globulin (HRIG), which may be unavailable following exposure

• Reduces vaccine doses from 5 to 3 doses

• Simplifies treatment from complicated 28 days to 3 days

• Increases protection if post-exposure prophylaxis (PEP) delayed

• Possibly protects against unreported or unrecognized exposure

• Reduces overall cost if treatment becomes necessary (pre-exposure prophylaxis + boosters = $1000, PEP + Human RIG = $4000)

• Decreases or eliminates chance of PEP failure* due to mistakes (studies performed on 28 PEP failures found 26 cases to have errors in PEP)

Pre-exposure rabies vaccine was initially developed by Louis Pasteur in the 1880s, by drying infected rabbit spinal cord to attenuate the rabies virus. Subsequently, vaccines were developed using nerve tissue and duck embryo. Brain-derived vaccine was associated with neuroparalytic reactions in >1/400 recipients. In the late 1970s, cell culture vaccines were developed: human diploid cell vaccine (HDCV), purified chick embryo culture vaccine (PCECV), purified Vero cell rabies vaccine (PVRV).

What is an adequate dosing schedule?

Adequate pre-exposure prophylaxis is given on a 3-dose schedule on days 0, 7, 21 or 28. Due to the expense of the vaccine, intradermal administration using a fraction of the intramuscular dose was introduced in the 1980s, but vaccines had to be used within hours of reconstitution. In 1986, manufacturers repackaged the vaccine into 0.1 ml individual syringe for intradermal administration. Ten studies in the 1970s-80s showed adequate antibody response, but antibody levels following intradermal administration were lower than intramuscular administration.

How long can you go?

Volunteers injected with 0.1 cc of rabies vaccine intradermally at 2 sites were tested at 1 year, and 13/16 had > 0.5 IU/ml. After a booster, the mean titer was 49+ at 2 weeks (good).[2] Minimum protective antibody level was considered to be 0.5 IU/ml according to the WHO, but this level should be interpreted as evidence of "boostability" rather than protection.

In 1983, a United States Peace Corps volunteer, a 23-year-old woman who had been immunized with the intradermal series was bitten by a puppy. No PEP was given, and she developed rabies 6 weeks later and died. A study of her cohort in Kenya found 9 of 11 had no seroconversion. Among Peace Corps volunteers in other countries, a 34%-40% failure rate was associated with intradermal rabies vaccines given in destination countries.[3] Hypotheses were tested regarding the failure, and suggested that concurrent administration of chloroquine reduced total immune response though antibodies still achieved adequate level.

When should boosters be given?

Anamnestic response persists for many years. In the 1980s, CDC advised boosters every 2 years. However, it is evident that the initial series produces boostability, and boostability lasts for years, as boostability is currently felt to last lifelong. No tourist has ever died while trying to get PEP, but tourists have died from no PEP or inadequate administration. Education is the key pre-travel measure.

Dr. Suvansrinon presented post-exposure diagnosis and treatment, focusing on human rabies deaths related to PEP in Thailand. She emphasized that WHO advocated strongly against neuro tissue rabies vaccines such as Semple.

Exposure categories (WHO) are:

• III - deep wounds, must have PEP

• II - minor scratch

• I - touching, feeding of animals or licks on intact skin

The WHO recommendations for PEP mandate wound cleansing, RIG and modern vaccines immediately.[4] The WHO approves of 4 rabies post-exposure vaccine schedules, 2 intramuscular and 2 intradermal regimens.

Table 1. Who Rabies Post-Exposure Vaccine Schedule

Type of Administration and Regimen	Abbreviation	Explanation
Intramuscular		
• **Essen**	**0, 3, 7, 14, 28**	**1 dose on days 0, 3, 7, 14, 28**
• Zagreb	2-1-1 (0, 7, 21)	2 doses on day 0, 1 dose on days 7 and 21
Intradermal		
• Oxford	8-0-4-0-1-1	Indicated for PVRV or PCECV; 0.1mL at 2 sites on days 0, 7, 21, and 1 site on days 30 and 90
• Thai Red Cross	2-2-2-0-1-1	Indicated for HDCV or PCECV; 0.1mL at 8 sites on day 0, 4 sites on day 7, 1 site on days 28 and 90

Among these, the Essen (administered on days 0, 3, 7, 14, and 28) is the regimen recommended and used in the United States.[4] (*See Table 1.*)

Dr. Suvansrnon discussed PEP failures and described a number of cases from 1985 to date. The reasons for failure included: 1) RIG was not used or not injected into all wounds; 2) vaccine or RIG were of poor quality; 3) a large viral load was inoculated through the bite; 4) virus was introduced into the nerve; 5) possible deviations from recommended dosing schedule. A sobering case for this associate editor was the case of an adult that was bitten by a dog, managed by observing the dog. The dog was suspected of having rabies on the 4th day. The patient received post exposure prophylaxis starting on the 6th day, but still succumbed to rabies. ■

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CME Questions

42. What is the risk of recurrent urinary tract infection among otherwise healthy children <6 years of age diagnosed with a first urinary tract infection?

A. <1% per year
B. 12% per year
C. 30-40%, almost all within 1 year
D. 30-40% per year
E. Almost 100% by 6 years of age

43. Which of the following is correct with regard to the BinaxNOW malaria test?

A. It has been demonstrated to be a reliable test with high sensitivity and specificity for the detection of infection with *P. malariae*
B. It can distinguish infection with *P. falciparum* from infection with other plasmodial species in patients without mixed infection.
C. False positive results never occur.
D. It entirely obviates the need for microscopy in the evaluation of patients with malaria.

44. Which of the following is correct with regard to Zika virus?

A. It is a flavivirus.
B. It is transmitted by ticks.
C. Infection with this virus has a high mortality rate.
D. Its most frequent manifestation is a severe encephalitis.

45. Immunoglobulin available for intravenous use (IVIG) from what geographic source has the best neutralizing capacity against West Nile Virus (WNV)?

A. Central America
B. Europe (pooled plasma)
C. U.S. (pooled plasma)
D. New Jersey

Answers: 42.(b) 43.(b) 44.(a)45.(c)

In Future Issues:

A Review of the Effects of Antiretroviral Agents on Lipid Panels of HIV-Positive Patients

UPDATES

By Carol A. Kemper, MD, FACP

Influenza — 2007/2008

Source: MMWR June 29, 2007, http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5606a1.htm

GUIDELINES FOR THIS YEAR'S influenza season are now available, with important recommendations to hospitals and clinics. The 2007/2008 trivalent vaccine contains A/Solomon Islands/ 3/2006 (H1N1-like), A/Wisconsin/ 67/2005 (H3N2-like), and B/Malaysia/ 2506/2004-like antigens. The A/Solomon Islands component, which a recent antigenic variant of the former A/Caledonia, is a new addition to the vaccine, while the other 2 antigens remain unchanged. While H1 viruses were more common during the peak season in February 2007, H3 viruses were more frequently identified later in the season in March through May. A few Influenza B viruses were also identified.

Vaccine coverage still falls below 50% for children, health care personnel, pregnant women, and adults with risk factors for influenza complications.

The target groups for vaccination have not changed. But the ACIP is re-emphasizing the following:

- Administration of 2 doses of vaccine to all children aged 6 months to 8 years;
- If children received only one dose in previous years, they should receive 2 doses this year. If they received two doses last year, then one dose this year is sufficient);
- Any one who requests vaccine should receive it; in other words, any one wishing to reduce their risk of influenza, even if they do not fall into a risk category, is a candidate for vaccination;

In addition, the ACIP strongly recommends:

- Health care facilities should offer immunization clinics throughout the flu season;
- Health care facilities should consider the level of vaccination among health care workers a patient safety quality measure.
- Health care facilities should implement policies such that health care workers refusing vaccination shall sign a declination. ■

Drug-induced Agranulocytosis

Source: Andersohn F et al. Systematic Review: Agranulocytosis induced by non-chemotherapy drugs. Ann Intern Med *2007;146:657-665.*

ONE OF MY LONG-STANDING HIV-infected patients returned to clinic last week with a surprising laboratory test result: he had acutely developed neutropenia with a white blood count of 2.3 with 13% granulocytes (absolute neutrophil count, ~0.3 x 10^9 cells/L). A quick review of his drug list included wellbutrin and amitrypfiline (he was not receiving antiretrovirals), revealed only one new addition to his regimen: terbenafine. Further investigation revealed another surprising finding: terbenafine has been rarely associated with agranulocytosis. He had received this agent in the past for 3 months with no difficulty.

Agranulocytosis (neutropenia < 0.5 x 10^9 cells/L) from antimicrobials, or from other drugs in patients receiving antimicrobials, is an infrequent but critical finding, often requiring Infectious Disease consultation. Antimicrobials are frequently suspect, chief among them penicillins and some cephalosporins, although there is limited evidence to support causality for many agents. For example, in observational studies, trimethoprim-sulfamethoxazole is included in the top 5 single agents associated with an increased risk for acute agranulocytosis, although based on case reports, these authors found only level 2 evidence to support an association with this agent.

These authors conducted a systematic review of 980 reported cases of non-chemotherapy drug-induced agranulocytosis since 1966, including the likely agents, the duration of drug exposure, the duration of neutropenia, and mortality. A total of 125 agents were definitely or probably related to acute agranulocytosis. Based on reported cases, 36 drugs had level 1 evidence and 89 drugs had level 2 evidence they were responsible for causing the acute agranulocytosis. More than half the cases were definitely or probably due to 11 of the agents (carbimazole, clozapine, dapsone, dipyrone, methimazole, penicillin G, procainamide, propylthiouracil, rituximab, sulfasalazine, and ticlopidine).

The median duration of treatment was a little as 2 days for dipyrone to 60 days for levamisole, and was longer than one month for three-fourths of the suspect agents. The time between presentation and normalization of neutrophil count ranged from 4 to 24 days. Six percent of cases were fatal, although patients who received Gm-CSF or G-CSF had a 5% fatality rate, and the case fatality rate decreased after 1990 once these drugs were available. Patients with a nadir neutrophil counts <0.1 x 10^9 cells/L had a significantly higher rates of infection (59% vs 39%), sepsis (20% vs 6%), and mortality (10% vs 3%) than those with higher nadir counts. Fortunately, the median duration of neutropenia was fairly short for most agents, including beta-lactam agents (ranging from 4 to 8 days).

It behooves each of us to be able to identify antimicrobial and non-antimicrobial agents with potential for caus-

ing neutropenia. In this review, terbenafine was associated with 5 reported cases of acute agranulocytosis, and was listed as having only level 2 evidence for causality. Improved reporting of cases and suspect agents would greatly enhance our databank. ■

Isolation and Quarantine for TB: What Rights Do You Have?

Source: Parmet WE. Legal power and legal rights - isolation and quarantine in the case of drug-resistant tuberculosis. N Engl J Med *2007;357(5);433-435.*

THE RECENT CASE OF THE ATLANTA attorney with active pulmonary tuberculosis who re-entered the United States against the "recommendation" of the CDC (assisted by an incredibly naive border guard) raised all kinds of questions in the press and among laypersons about the legal authority of the states and the federal government to isolate or quarantine individuals. Heretofore many individuals were unaware of this authority, which some found imperative and reassuring, and others saw as a part of an emerging threat to civil liberties. Mr. Andrew Speaker's case struck at the heart of American society: when does the common good of the public outweigh the rights of the individual?

This interesting article highlights some of the history and issues regarding that authority, which I learned is not unfettered and subject to judicial oversight. Firstly, there is a difference between isolation of an individual who is known to be contagious, and quarantine of goods or individuals who may have been exposed to a contagious disease. While we isolate individuals with TB, patients potentially exposed to SARS, for example, are quarantined. Both may be done on a voluntary basis or, if necessary, forcibly. Both the states and federal government have the authority to compel either action, although generally the federal government's role is limited to goods or individuals entering the country or crossing state lines (as in Mr. Andrew Speaker's case).

Importantly, retained individuals have a right to a court review of their detention's legality. While the courts generally give deference to state authority in the isolation of patients with tuberculosis, the courts have stipulated a number of conditions, including that such individuals retain the right to counsel and to a hearing by an independent decision maker. Constitutional guarantees of equal protection and due process are protected. For example, in New York, 90% of patients isolated for tuberculosis in the 1990s were non-white and 60% were homeless, raising concerns that isolation practices were being unfairly applied — although those may the very groups most affected by MTb. However, the potential for discrimination reinforces the need for judicial oversight, at least to ensure public trust.

Some courts have held that the government must provide "clear and convincing" evidence of public health risk. Unfortunately, what has not been clarified is the duration of detention before a hearing is required, what probability of risk justifies isolation, how infectious a person must be to justify isolation, and what procedures are considered "legal" if mass quarantine is required (e.g., for avian influenza or SARS).

In addition, some courts have specified that the government is responsible for providing the least restrictive alternative for preventing a public health risk. Because states have argued that a failure to comply with directly observed therapy was the basis for forcible detection, the courts left open the possibility that compulsory isolation may not be constitutional in states that do not provide directly observed therapy. In Mr. Speaker's case, when contacted by the CDC in Italy and asked to voluntarily report to authorities in Rome, what was the obligation of the Federal Government to provide him safe passage home in order to consider him non-compliant? During the SARS outbreak in Toronto, the government largely relied on voluntary quarantine, but provided social support and compensation for quarantined persons, making voluntary quarantine more feasible.

Since 9-11, newer federal regulations, which are still being reviewed, have clarified and expanded the government's authority for compulsory detention for isolation or quarantine. This entails short-term detention of individuals for up to 3 business days without access to legal representation or a court hearing. Individuals subject to non-provisional quarantine would still retain the right to a hearing but no attorney would be provided and there would not be an independent decision maker. Furthermore, the CDC would be able to isolate individuals without first having to demonstrate a significant public health risk or provide a least restrictive alternative.

While this may make sense in certain circumstance, where insufficient data exists or is not yet available but a threat is believed by authorities to be considerable and legitimate, it nonetheless makes civil libertarians quite nervous. Without the necessary teeth to exercize their authority, how can we expect public health officials to respond when needed? e.g., try taking 100 people on a plane from Taiwan, landing in San Jose, to the closest hospital for evaluation, and eventual quarantine, because 2 people on board might have SARS (which, in reality, took months to confirm). How about when the appropriate laboratory tests don't even exist? I suspect that (at least) the U.S. public is unprepared for a disaster, naive to the complexities of infectious disease outbreaks (learned best from the movie "Outbreak" — just give me the antis-era), and presume the government will oversee their safety without impinging on their individual rights. ■

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.

Oral Anticoagulant + Antiplatelet Therapy = Danger

In this issue: *Adding an anticoagulant to aspirin is of no value in patients with peripheral artery disease, older adults with coronary disease benefit from aggressive statin therapy, simvastatin may reduce the risk of dementia and Parkinson's disease by as much as 50%, MiraLAX is safe for long-term use in patients with chronic constipation, the FDA greenlights Avandia, brings back Zelnorm for limited use, and recommends approving Evista for breast cancer prevention.*

Patients with peripheral artery disease are at high risk for cardiovascular complications. Antiplatelet drugs are routinely prescribed for these patients, but is adding an oral anticoagulant of value? No, according to a new study. In fact, the combination may be dangerous. More than 2,100 patients with PAD were randomly assigned to antiplatelet therapy with an oral anticoagulant or to antiplatelet therapy alone. The first coprimary outcome was myocardial infarction, stroke, or death from cardiovascular causes. The second coprimary outcome was myocardial infarction, stroke, severe ischemia of the peripheral or coronary arteries leading to urgent intervention or death from cardiovascular causes. After an average followup of 35 months, the first coprimary outcome occurred in 132 of 1080 patients receiving combination therapy (12.2%) and 144 of 1081 patients receiving antiplatelet therapy alone (13.3%) (RR 0.92; 95% CI, 0.73 to 1.16; $P = 0.48$). The second coprimary outcome occurred in 172 patients receiving combination therapy (15.9%) compared to 188 patients receiving antiplatelet therapy alone (17.4%) (RR 0.91; 95% CI, 0.74 to 1.12; $P = 0.37$). Life-threatening bleeding occurred in 43 patients receiving combination therapy (4.0%) as compared to 13 patients receiving antiplatelet therapy alone (1.2%) (RR 3.41; is 95% CI, 1.84 to 6.35; $P < 0.001$). The authors conclude that adding an oral anticoagulant to antiplatelet therapy in patients with PAD was not more effective than antiplatelet therapy alone in preventing major cardiovascular complications, but was associated with an increase in life-threatening bleeding (*N Engl J Med* 2007; 357: 217-227). ■

High-Dose Statin Therapy, Value for Older Adults

Aggressive lipid lowering with high-dose statin therapy may be of value in older adults with stable coronary disease. The multicenter study from the United States included 3,809 patients 65 years or older with coronary artery disease and cholesterol levels less than 130 mg/dl who were randomized to receive atorvastatin 10 mg or 80 mg. Patients on low-dose atorvastatin achieved average cholesterol levels of 100 mg/dl versus 70 mg/dl for high dose therapy. The primary endpoint was occurrence of first major cardiovascular event such as death from CHD, nonfatal non-procedure-related myocardial infarction, resuscitated cardiac arrest, or fatal or nonfatal stroke. Patients treated with high-dose atorvastatin were found have a 2.3% absolute risk reduction and a 19% relative risk reduction for the primary endpoint (hazard ratio 0.81 [95% CI, 0.67 to 0.98]; $P = 0.032$). Mortality rates were

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lower for CHD, nonfatal non--procedure-related myocardial infarction, and stroke in the high-dose group. High-dose therapy was not associated with elevated creatine kinase levels. The authors conclude that treating older patients with coronary heart disease more aggressively to reduce low-density lipoprotein cholesterol levels provides additional clinical benefit (*Ann Int Med* 2007;147: 1-9). ■

Simvastatin, Best for Parkinson's Disease

Simvastatin, not atorvastatin or lovastatin, is associated with a dramatically reduced risk of dementia and Parkinson's disease (PD) according to a study from Boston University and VA database of 4.5 million individuals (95% men). In the observational study, over 700,000 subjects took simvastatin, nearly 54,000 took atorvastatin, and over 54,000 patients were prescribed lovastatin. Three models were used to evaluate the data, adjusting for covariates associated with dementia or Parkinson's disease. The first model was adjusted for age; the second model adjusted for 3 known risk factors for dementia: hypertension, cardiovascular disease, or diabetes; and the third model adjusted using the Charlson index, an index that provides broad assessment of chronic disease. Using the third model, the hazard ratio for dementia was 0.46 for simvastatin (CI 0.44-0.48, $P < 0.0001$) and 0.91 for atorvastatin (CI 0.80-1.02, $P = 0.11$). Lovastatin was not associated with a reduction in the incidence of dementia. The hazard ratio for newly acquired Parkinson's disease was 0.51 for simvastatin (CI 0.49-0.55, $P < 0.001$). There was no reduction in PD with atorvastatin or lovastatin. The degree of risk reduction utilizing the other models was similar with simvastatin. The authors conclude that simvastatin is associated with a strong reduction in the incidence of dementia and PD, while atorvastatin is associated with a modest reduction in incidence of dementia and Parkinson's disease that shows a trend toward significance (*BMC Med* published online July 19, 2007). The surprising finding suggests a difference between simvastatin and atorvastatin out of proportion to their cholesterol lowering effects, which the authors suggest may be due to the ability of simvastatin to cross the blood brain barrier more readily than other statins. ■

Polyethylene Glycol for Chronic Constipation

Long-term use of polyethylene glycol is safe and effective for chronic constipation according to the results of a new study from Alabama. More than 300 patients were randomized to receive polyethylene glycol 3350 (MiraLAX) in a single 17 g dose per day or placebo for 6 months. The primary endpoint of improvement of constipation on an objective scale was reached in 52% of the PEG patients and 11% placebo patients ($P < 0.001$). Similar efficacy was seen in a subgroup of 75 elderly patients. There were no significant adverse events other than diarrhea, flatulence and some nausea associated with PEG. The authors conclude that PEG laxative is safe and effective for use in patients with chronic constipation for up to 6 months (*Am J Gastroenterol* 2007;102:1436-1441). The study is particularly important because MiraLAX is now available over-the-counter and long-term use by patients with chronic constipation is likely. ■

FDA Actions

The FDA's Oncologic Drugs Advisory Committee, on a narrow vote, recommended approval of raloxifene (Evista) for the indication of breast cancer prevention in high risk women. The approval was based on data from the Study of Tamoxifen and Raloxifene (STAR) trial, which showed a reduction of 4 cases of breast cancer per 1,000 women (50% relative risk reduction), although it was not as effective as tamoxifen in preventing noninvasive breast cancers. Similar findings were seen in the Raloxifene for Use for The Heart (RUTH) trial although this trial revealed a higher risk of fatal stroke and blood clots with raloxifene. The FDA generally follows its advisory committee recommendations. Raloxifene is already approved for the prevention of osteoporosis.

The FDA has approved restricted use of tegaserod (Zelnorm) for the treatment of irritable bowel syndrome with constipation and chronic idiopathic constipation in women under the age of 55 who meet certain criteria. The drug was taken off the market earlier this year when it was linked with a higher risk of cardiovascular events including heart attack, stroke, and unstable angina. Patients must have no history of heart disease and must be in critical need of the drug. Prescribing will be under an investigational new drug protocol program that has been set up by the FDA.

Rosiglitazone (Avandia-GlaxoSmithKline) is associated with an increase risk of heart failure and myocardial infarction. Despite this, the FDA's Endocrinologic and Metabolic Drugs Advisory committee along with the Drug Safety and Risk Management Advisory Committee has advised that the drug stay on the market, albeit with increased warnings. Type 2 diabetes patients who are on insulin for those with heart disease are not the candidates for the drug. The FDA will render a final decision on the drug this fall. ■