AHC Media

Vol. 31, Issue 8, May 2012
www.ahcmedia.com

Infectious Disease [ALERT]

A monthly update of developments in infectious disease, hospital epidemiology, microbiology, infection control, emporiatrics, and HIV treatment

ABSTRACT & COMMENTARY

TB in the U.S. — Things Continue to Improve, But There is a Long Road Ahead

By Stan Deresinski, MD, FACP, FIDSA

Clinical Professor of Medicine, Stanford University, Associate Chief of Infectious Diseases, Santa Clara Valley Medical Center, is Editor for Infectious Disease Alert.

SOURCE: CDC. Trends in tuberculosis – United States, 2011. *MMWR* 2012; 60:181-5.

Based on reports to the CDC National Tuberculosis Surveillance System, the rate of new TB cases in 2011 was the lowest since reporting began in 1953. A total of 10,521 cases were reported in 2011 for an incidence of 3.4 cases per 100,000 population — a decrease of 6.4% from the previous year.

RACE/ETHNICITY

While the incidence decreased in all racial and ethnic groups, in Asians it decreased by only 0.6%. while in non-Hispanic whites it decreased by 6.2%. In Hispanics the decrease was 7.2% and in non-Hispanic blacks it was 10.2%. Despite these reductions, the rate of incident cases (both new infection and reactivation disease) was 12 times higher in foreign-born individuals than in those born in the U.S. These relative changes in incidence led to Asians passing Hispanics as the largest group with TB for the first time since the current reporting system was instituted in 1993. Five countries of origin accounted for 54.1% of cases among foreign born: Mexico, the Phillipines, Vietnam, India, and China. The TB rate in (non-Hispanic) Asians was 7 times higher than in Hispanics, 8 times higher than in non-Hispanic blacks, and 25 times higher than in non-Hispanic whites. Among only U.S.-born groups, however, the rate of TB relative to non-Hispanic whites was greatest for non-Hispanic blacks whose rate was 6 times higher. Overall, the rate in all U.S.-born individuals was only 1.5 cases per 100,000 population, a 10.3% decrease since 2010 and an 80.1% decrease since 1993.

THE STATES

The rates of TB per 100,000 population ranged from 0.7 in Maine to 9.3 in Alaska. Despite the overall decrease, 16 states and the District of

Financial Disclosure: *Infectious Disease Alert*'s editor, Stan Deresinski, MD, FACP, FIDSA, does research for the National Institutes of Health, and is an advisory board member and consultant for Merck; Updates author, Carol A. Kemper, MD, FACP, does research for Abbott Laboratories and Merck; and peer reviewer Timothy Jenkins, MD, reports no financial relationship to this field of study.

Infectious Disease [ALERT]

Infectious Disease Alert,
ISSN 0739-7348, is published monthly by AHC Media, a division of Thompson Media Group LLC, 3525 Piedmont Road., NE Building 6, Suite 400 Atlanta, GA 30305.

POSTMASTER: Send address changes to *Infectious Disease Alert*, P.O. Box 105109, Atlanta, GA 30348.

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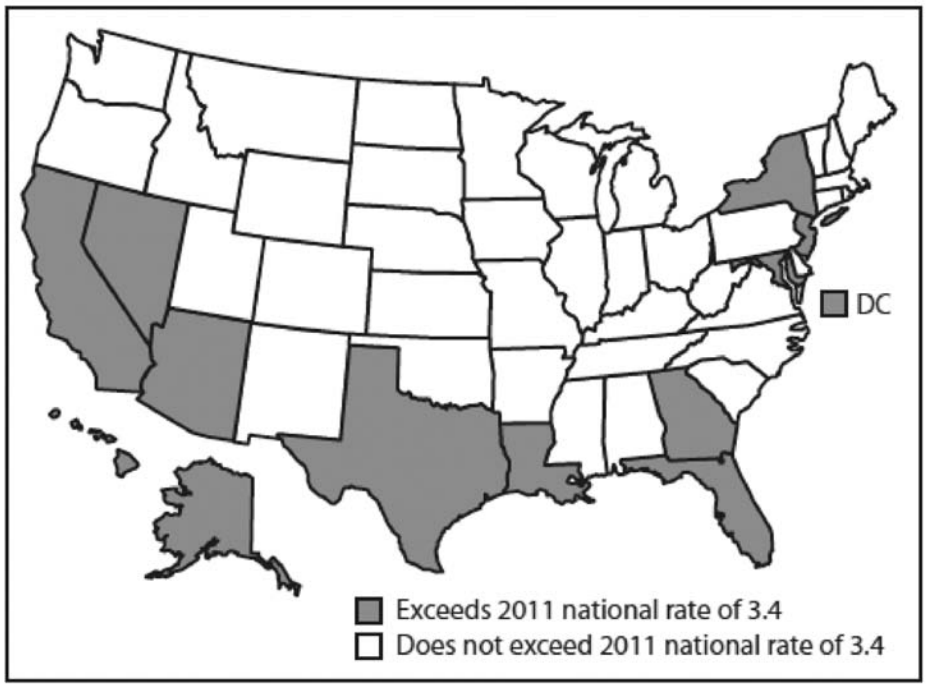
FIGURE 1. RATE* OF TUBERCULOSIS CASES — UNITED STATES, 2011†



* Per 100,000 population.

† Data are provisional.

Alternate Text: The figure above shows the rate of tuberculosis (TB) cases in the United States, during 2011. Compared with the national TB case rate of 3.4 cases per 100,000 population, TB rates in reporting areas ranged widely, from 0.7 in Maine to 9.3 in Alaska (median: 2.4).

Columbia had higher rates in 2011 than in 2010 *(See Figure 1)*. Four states — California, Florida, New York, and Texas) accounted for approximately one-half of all TB cases reported in 2011.

HIV STATUS, MDR TB, XDR TB

Among the 81% of cases for whom their HIV status was known, 7.9% were seropositive. A total of 109 cases of MDR TB were reported in 2010 (the most recent year for which complete results were available), representing 1.3% of those tested, a figure unchanged from the previous year. Among individual with no past history of treatment for tuberculosis, the percentage of MDR TB has remained stable at approximately 1.0% since 1997. Among those with a previous history of TB, the proportion with MDR TB was approximately 4 times higher. Foreign-born individuals accounted for 82.6% of the total MDR TB cases in 2010 and 4 cases of XDR TB have were reported in 2011, all occurring in foreign-born.

■ COMMENTARY

These data indicate that, while the overall rates of tuberculosis are progressively decreasing in the U.S., TB continues to be a significant problem, especially among the foreign-born. Among the latter, Asians represent the group with the single highest incidence and the smallest year-to-year decrease. Almost 80% of cases among the foreign-born were diagnosed 2 or more years after entry into the U.S., suggesting that most were the result of reactivation of latent infection that had been acquired in their native lands. This observation supports an aggressive approach toward the detection and treatment of latent TB, something that may be facilitated by the use of once weekly directly observed treatment with rifapentine and isoniazid.

Despite this largely good story of a progressive decrease in the incidence of TB, it is estimated that, unless current efforts are improved and/or expanded, the goal of TB elimination in the U.S. will not be reached before the turn of

the next century. As stated by CDC, "Initiatives to improve awareness, testing, and treatment of latent infection and TB disease in minorities and foreign-born populations might facilitate progress toward the elimination of TB in the United States. Progress toward TB elimination in the U.S. will require ongoing surveillance and improved TB control and prevention activities. Sustained focus on domestic TB control activities and further support of global TB control initiatives is important to address persistent disparities between non-Hispanic whites and racial/ethnic minorities and between U.S.-born and foreign-born persons."

Whether this can be accomplished in the current economic and political climate is uncertain, at best. The recent report of an outbreak of pulmonary TB in 26 homeless individuals with a chain of transmission from 2007-2011[1] is a case in point. In November 2010, while the outbreak was still going on (although it remained occult), the local public health department's workforce was reduced by 50%. Once before, TB control activities were reduced in this country, a move that was followed by a resurgence of case rates in the U.S. — will we ever learn? ■

Reference

1. CDC. Tuberculosis outbreak associated with a homeless shelter – Kane County, Illinois, 2007-2011. *MMWR* 2012; 60:186-9.

ABSTRACT & COMMENTARY

Nasopharyngeal Bacterial Changes with Antimicrobials and Pneumococcal Vaccine

By Hal B. Jenson, MD, FAAP

Dean, School of Medicine, Western Michigan University School of Medicine, Kalamazoo, MI., is Associate Editor for Infectious Disease Alert.

Dr. Jenson reports no financial relationships relevant to this field of study.

SYNOPSIS: Antimicrobial use and heptavalent pneumococcal vaccine induce significant changes in the nasopharyngeal microbiota of young children, with reduced prevalence of *Streptococcaceae* and *Corynebacteriaceae* and increased prevalence of *Enterobacteriaceae* and *Pasteurellaceae*.

SOURCE: Hilty M, Qi W, Brugger SD, et al: Nasopharyngeal microbiota in infants with acute otitis media. *J Infect Dis* 2012;205:1048-1055.

A total of 153 nasopharyngeal swabs were collected as part of a nationwide study in Switzerland from children <2 years of age treated for acute otitis media from 2004-2009. Approximately one-quarter of young children with acute otitis media had been treated recently with antimicrobials, approximately one-third attended day care, and approximately half had received heptavalent pneumococcal vaccine (PCV7). An additional 10 specimens were collected from young children without acute otitis media as controls. Nasopharyngeal microbiota was characterized using multiplexed pyrosequencing targeting the variable regions 3—5 of the 16S rRNA gene.

Operational taxonomic units of microbiota were identified with a minimum of 97% sequence identity, and were grouped into 58 bacterial families. The median Shannon Diversity indices were 0.69 for young children with acute otitis media and 1.31 controls (P = 0.002), indicating that young children with acute otitis media have fewer microbiota taxonomic units and that were less evenly distributed than for controls. The most commonly identified bacterial families were *Moraxellaceae* (present in 154 of 163 specimens), non-pneumococcal *Streptococcaceae* (122 of 163), and Pasteurellaceae (97 of 163). Commensal families were more frequent in controls than in young children with acute otitis media, such as *Staphylococcaceae* (P = 0.001), *Flavobacteriaceae* (P = 0.0004), *Carnobacteriaceae* (P = 0.02), and *Comamonadaceae* (P = 0.003). Young children with recent exposure to microbials also less frequently carried *Streptococcaceae* (P = 0.02) and *Corynebacteriaceae* (P = 0.001), and more frequently carried *Enterobacteriaceae* (P = 0.03). Young children who had received PCV7 less frequently carried *Corynebacteriaceae* (P = 0.02) than did unvaccinated children. Further analysis showed that the differences of microbiota between children with acute otitis media and

controls were due to the prevalence of bacterial families (unweighted analysis) rather than their relative abundance (weighted analysis).

Colonization density was estimated by measuring the DNA concentration of the PCR application product. Significantly lower quantities of total DNA were observed from controls (median, 12 ng/μL) compared to young children with acute otitis media (median, 38 ng/μL; P = 0.005).

There was no influence of age, history of recurrent acute otitis media, sex, or day care attendance on the microbiota of young children with acute otitis media.

■ COMMENTARY

Normal nasopharyngeal microbiota among young children is characterized by commensal bacterial families and non-pneumococcal *Streptococcaceae*. Among young children with recent antimicrobial exposure, classic otitis media pathogens predominate over the commensals, resulting in reduced richness and evenness but higher overall colonization density. Vaccination with PCV7 changed the community structure of microbiota towards reduced prevalence of commensals, especially Streptococcaceae and Corynebacteriaceae.

Antimicrobial treatment of acute otitis media, and for that matter antimicrobials used for other reasons, has important effects on the nasopharyngeal microbiota among young children. Antimicrobials lead to the displacement of a broad array of nonpathogenic nasopharyngeal commensals with a narrower spectrum of pathogenic organisms and with higher density of organisms. This is a vicious circle, in which treatment of the initial episode of otitis media results in nasopharyngeal microbiota changes that are likely predisposed to subsequent episodes. ■

Reference

Weinberger, DM , et al. Impact of the 2009 Influenza Pandemic on Pneumococcal Pneumonia Hospitalizations in the United States. *J Infect Dis* 2012:205:458-465

ABSTRACT & COMMENTARY

Age of Primary Epstein-Barr Virus Infection Affects Immune Control

By Hal B. Jenson, MD, FAAP
Dean, Western Michigan University School of Medicine, Kalamazoo, MI., is Associate Editor for Infectious Disease Alert.

Dr. Jenson reports no financial relationships relevant to this field of study.

SYNOPSIS: Younger age of infection with Epstein-Barr virus occurs in areas of high malaria burden and results in higher viral loads throughout the first 2 years of life that is associated with increased risk for Burkitt lymphoma.

SOURCE: Piriou E, et al: Early age at time of primary Epstein-Barr virus infection results in poorly controlled viral infection in infants from western Kenya: Clues to the etiology of endemic Burkitt lymphoma. *J Infect Dis* 2012;205:906-13.

Infants in an area with high malaria exposure were infected with EBV at a significantly younger age in infancy, with a much higher incidence of primary EBV infection before 6 months of age. They also had EBV DNA detected more frequently and at higher levels throughout the first two years of life, indicating poor control of EBV infection.

Two cohorts of children in Kenya, one from an area of high malaria transmission and high risk for Burkitt lymphoma and the second from an area of low malaria transmission and low risk for Burkitt lymphoma, were enrolled in 2006. Children were studied prospectively for age of primary Epstein-Barr virus (EBV) infection with blood samples collected at 1 month of age and then every month through 12 months of age, and every 4 months through 24 months of age. EBV DNA was detected by quantitative polymerase chain reaction, and antibody testing was performed using a luminex bead-based assay for VCA-IgM, VCA-IgG, and EBNA1-IgG. Only children born to HIV-uninfected mothers were enrolled.

At the end of 2 years, retention rates were 64% and 78% in the two cohorts, with a total of 150 children completing the study. The age of primary EBV infection was defined as detection of any marker of EBV infection:

EBV-DNA, or a 2-fold increase over a previous sample (to account for maternal antibodies) in VCA-IgM, VCA-IgG, EBNA1-IgG, or EBV DNA.

Children born in the region at higher risk of Burkitt lymphoma showed earlier age at time of primary EBV infection (7.28 months +/- 0.33 SEM vs. 8.39 months +/- 0.26 SEM), including higher rate of EBV infection before 6 months of age (35.3% vs. 12.2%; P<0.0001). These children also had significantly higher EBV viral loads based on tie-averaged area under the curve (1.28 log10 copies/µg vs. 0.78 log10 copies/µg; P<0.002).

■ COMMENTARY

Endemic Burkitt lymphoma is the most common childhood malignancy in Saharan Africa, and has been linked to EBV infection. The geographic overlay of Burkitt lymphoma with malaria suggests that malaria is also an important cofactor in the etiology of Burkitt lymphoma. The interplay of EBV causality and the geographic association of malaria for Burkitt lymphoma is unclear.

This study shows that infants in an area with high malaria exposure were infected with EBV at a significantly younger age in infancy, with a much higher incidence of primary EBV infection before 6 months of age, and also had EBV DNA was detected more frequently and at higher levels throughout the first two years of life, indicating poor control of EBV infection. This finding is similar to other viral infections occurring during early infancy, such as hepatitis viruses and cytomegalovirus.

Collectively, these data indicate that early age of primary EBV infection leads to poor control of EBV infection, and is a risk factor for development of endemic Burkitt lymphoma. It is plausible that malaria exposure and infection facilitates early age of EBV infection, which results in poor immunological control of the infection. The association of EBV with several forms of human cancer — Burkitt lymphoma, nasopharyngeal carcinoma, and Hodgkin disease, as well as leiomyosarcoma in immunocompromised persons — underscores the importance and the potential benefits of developing a vaccine strategy against EBV. ■

PHARMACOLOGY UPDATE

Ivermectin Lotion 0.5% (Sklice™)

This article originally appeared in the March 29, 2012 issue of Internal Medicine Alert.

By William T. Elliott, MD, FACP, and James Chan, PharmD, PhD

Dr. Elliott is Chair, Formulary Committee, Northern California Kaiser Permanente; and Assistant Professor of Medicine, University of California, San Francisco.
Dr. Chan is Pharmacy Quality and Outcomes Manager, Kaiser Permanente, Oakland, CA.

Drs. Elliott and Chan report no financial relationships relevant to this field of study.

A new topical preparation for the treatment of head lice has been approved by the FDA. Ivermectin is a macrocyclic lactone antibiotic that has been used orally both on and off label for head lice since 2001. This new formulation is a topical lotion (oral invermectin is not approved in the United States). It is manufactured by DPT Laboratories and is distributed by Sanofi Pasteur, Inc., as Sklice.

INDICATIONS

Ivermectin lotion is indicated for the topical treatment of head lice infestation in patients 6 years of age and older.[1]

DOSAGE

Ivermectin is applied as a single 10-minute application to the hair and scalp. It is available as a 0.5% lotion.

POTENTIAL ADVANTAGES

Ivermectin solution is well tolerated and provides another option for the treatment of head lice.

POTENTIAL DISADVANTAGES

Approximately 25% of those treated with topical ivermectin were not lice free. It may be less effective than other products (e.g., spinosad or oral ivermectin).

COMMENTS

Ivermectin is believed to cause paralysis and death of mites by selective binding to glutamate-gated chloride channels.[1] Its efficacy was shown in two randomized, vehicle controlled studies in subjects with head lice.[1] The youngest subject from each household was the primary subject for assessment of efficacy. Other members were evaluated for safety. All infected subjects were randomized to ivermectin or vehicle only as a single application. The primary endpoint was percent free of lice 14 days after application. The results from the two studies were 76.1% (54/71) and 71.4% (50/70) for ivermectin compared to 16.2% (12/74) and 18.9% (14/74) for the vehicle. Ivermectin appears to be well tolerated as adverse reactions (conjunctivitis, ocular hyperemia, eye irritation, dandruff, dry skin, and skin burning sensation) occurred in fewer than 1% of subjects.[1] There are no published comparative studies with other topical agents such as permethrin, benzyl alcohol, malathion, spinosad, or oral ivermectin. For rough comparisons, the cure rate (lice free in 2 weeks) of approximately 74% compared to 44%-68% for permethrin, 76% for benzyl alcohol, 85% for spinosad, 85%-98% for malathion, and 95% for oral ivermectin.[2-5]

CLINICAL IMPLICATIONS

Head lice is a common infestation in children ages 3-12.[6] Permethrin is commonly used but generally requires two applications. Benzyl alcohol and spinosad need one application with success rates at least as good as topical ivermectin. ■

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CASE REPORT & COMMENTARY

Cystic Cerebellar Lesions Post Honeymoon: A Strange Case of Neurocysticercosis

This article originally appeared in the April 2012 issue of Travel Medicine Alert.

By Maria D. Mileno MD

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

Dr. Mileno reports no financial relationships relevant to this field of study.

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

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

Case Summary: A 27-year-old physical education teacher presented with two separate episodes of ill-defined dizziness and mild confusion over a period of one week. He was in good health, except for numerous upper respiratory infections during the months prior to his onset of dizziness. The first episode occurred while he was working in his basement. He described a feeling of "spaceyness" with difficulty forming words. This lasted roughly 90 minutes. He did not lose consciousness. The second episode occurred while he was playing basketball at the school where he is a physical education teacher, and it was quite similar to the first episode. The school nurse evaluated him and found an elevated blood pressure. He was sent by ambulance for hospital evaluation of hypertension and dizziness at which time CT imaging and an MRI revealed cystic cerebellar lesions. He had neither focal neurological symptoms nor fever in association with these episodes, and no nausea nor vomiting. Clinically the episode seemed most consistent with

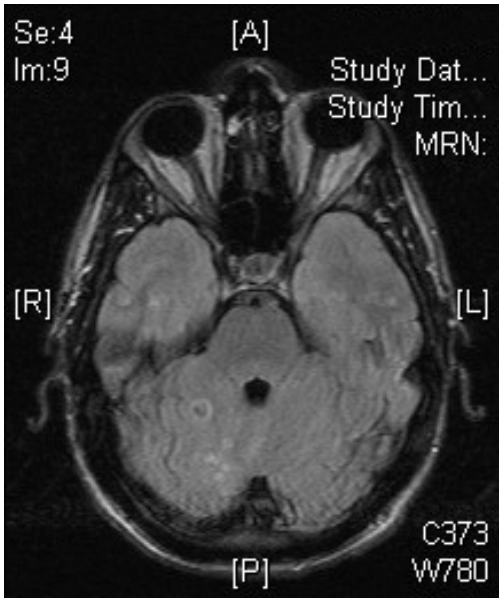

Fig. 1A: MRI scanning and imaging of initial cerebellar lesions

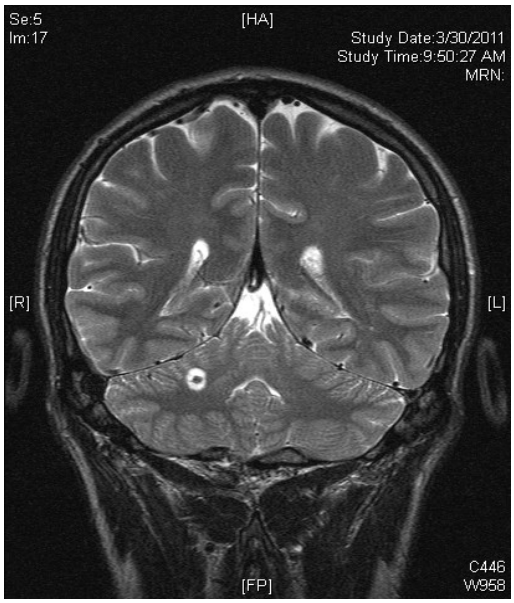

Fig. 1B: MRI scanning and imaging of initial cerebellar lesions

either a seizure aura or a true seizure. *(1A)* Further neurosurgical evaluation excluded a brain tumor, stroke or seizure disorder based upon his clinical examination, an EEG and the MRI appearance *[see Fig 1A and 1B]* of his lesions. He was referred for an outpatient infectious disease consultation to evaluate these symptoms and for further management of probable neurocysticercosis.

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

An initial CT scan [not shown here] identified 2 small focal defects in the right cerebellum measuring 0.6 and 1.1 cm in diameter. The MRI scan shows the extent of the brain involvement without cerebral lesions. *(See Fig 1A and 1B.)* The T2 weighted images showed a focus of five or six rounded areas of bright signal in the right posterior fossa of the cerebellum, the largest measuring approximately 8 mm with an internal nodular septate appearance. Post-gadolinium imaging showed a tiny nodule enhancing at the midparietal level to the right of the midline, not shown in this image. *(1B)*
Serological tests for cysticercosis were forwarded to the CDC, but given his ongoing symptoms and known risk of brain edema during treatment he was hospitalized for pre-treatment with dexamethasone and praziquantel 100 mg/kg/d, in 3 divided doses. He tolerated this well, but required diphenhydramine for skin redness with administration of his praziquantel. He completed 2 weeks of high dose corticosteroids. Almost daily he continued to have episodes of the "strange feeling" he found difficult to describe. Things seem to be "happening fast" and vision during this 10-minute period was less focused. He had to look away then refocus on TV for example. No loss of consciousness occurred. Episodes were sometimes more intense than his original presentation, but similar in nature. Final serological tests, including the Immunoblot assay for cysticercosis antibodies performed at CDC were negative. Upon follow up with the patient 6 months later *(See Fig 2)* he was well and without further episodes.

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

Other neurocysticercosis cases reported

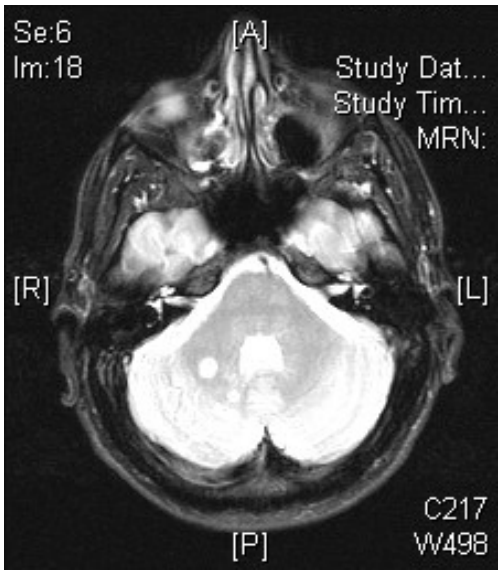

Fig. 2: MRI 6 months post treatment showing calcified lesions in the cerebellum, no new lesions remaining.

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

■ COMMENTARY

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

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

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

Single-day praziquantel treatment regimens with favorable results have been published. They allowed us to complete anti-parasitic treatment during a short inpatient stay, followed by a prolonged course of cortiosteroids for two additional weeks to produce continued eradication of the parasites.

The paper by Leshem et al offers numerous references that explore the magnitude of neurocysticercosis as an emerging infection, and the various approaches to disease management in the summaries of case reports. The spectrum of treatment options has ranged from no treatment to neurosurgery and a panel of experts wrote consensus guidelines to set some basic principles of therapy.[3] They concluded that each case must be individualized. Anti-parasitic agents should not be used in those cases showing already calcified parasites or during cysticercosis encephalitis. Importantly, antiparasitic treatment should be used to treat actively growing cysts and pre-treatment corticosteroids should be utilized, as well as anti-seizure medications. A growing lesion may require surgical excision. Cysts located in the ventricular system should be treated surgically if the necessary neuroendoscopic techniques are available. When hydrocephalus or intracranial hypertension is present management using a ventricular shunt is the top priority.
We had the benefit of follow-up neuroimaging technique. On a worldwide basis this may not be available nor performed for economic reasons. There are no studies showing long-term outcomes for neurocysticercosis. This case, in conjunction with the series published by Leshem et al, provides follow up that should be reassuring about the favorable course of this disease with medical management.[4] ■

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ABSTRACT & COMMENTARY

Dengue in Pediatric Travelers

This article originally appeared in the April 2012 issue of Travel Medicine Alert.

By Philip R. Fischer, MD, DTM&H
Dr. Fischer is Professor of Pediatrics, Department of Pediatric and Adolescent Medicine, Mayo Clinic, Rochester MN.

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

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

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

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

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

■ COMMENTARY

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

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

Four distinct serotypes of dengue virus cause human infection.[4] Typically, severe disease occurs in individuals who have also had previous dengue infection with a different dengue serotype. It is thought that antibody enhancement of the second infection superimposed on existing sero-specific immunity triggers an exaggerated cytokine response with capillary leak and severe illness.[4,5] Interestingly, as seen in this new report from the Bronx and in pediatric populations in dengue-endemic areas, the dengue shock syndrome form of illness is often seen in infants during the second half of the first year of life. Perhaps this is due to interactions between the child's primary dengue infection and waning maternal antibodies that had been acquired transplacentally. Another recent report, however, revealed that adult travelers could have significant ultrasonic evidence of capillary leakage even with primary dengue infection that presented without severe illness.[6]

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

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Updates

By Carol A. Kemper, MD, FACP

Worldwide Surgical Need Unmet

Groen RS, et al. The unmet surgical disease burden in the developing world (letter). *The Lancet* 2012; vol 379: 616.

In response to concerns that too much, and possibly unnecessary, surgery is undertaken in developing countries, especially in the elderly, these authors remind us that the vast majority of people around the globe requiring surgery don't get it.

The WHO website indicates that out of 234 million surgeries performed annually worldwide, 73.6% are performed in the world's richest one-third and only 3.5% are performed in the poorest third. This lack of access to surgical expertise means that many patients with a surgically-reversible problem may die. For example, recent data from Sierra Leone found that 7% of individuals surveyed needed a surgical evaluation or procedure. In the previous 12 months, 22% of deaths were attributed to a lack of necessary surgical attention.

A group called Surgeons Overseas (SOS) has been attempting to document and raise awareness of the unmet surgical need around the world, through a collaborative effort called the Surgeons Overseas Association of Surgical Need. Their aims are to increase the long term surgical capacity, especially in the areas of greatest unmet need, provide protective equipment for operating room personnel (to reduce the risk of blood borne pathogen transmission), to help provide supplies and equipment, and to provide basic training and education of local individuals for basic surgical emergencies and trauma. Sadly, many health care workers and OR personnel in developing countries are at increased risk for hepatitis and HIV, because of a lack of even basic personal protective gear. Remedying that problem would save trained personnel in these countries. *(The SOS website is www.humanitariansurgery.org.)* ■

Cephalosporins banned in Cattle and Pigs

Voelker R. FDA: Limited ban on cephalosporin use in major food-producing animals. *JAMA* 2012; 307 (5): 443.

The use of antibacterials in food-animals has been ongoing ever since antibiotics were discovered. I remember my mother refused to eat turkey years ago because they would inject them with high doses of long-acting penicillin prior to slaughter. She claimed she was allergic to the residual PCN in the meat (or maybe she just did not like turkey).

Given concerns over the increased risks of selective pressure for bacterial resistance, the United States Food and Drug Administration (FDA) has issued an order, effective April 5th, prohibiting the use of cephalosporins in major food animals (swine, cattle, chickens, and turkeys) for any use not previously approved. Specifically, the ban covers the use of cephalosporins for "extra-label" uses at any dose, frequency, or duration, unless previously approved; the use of these agents in major food animals for purposes not previously approved for that species; and the use of cephalosporins for disease prevention. For example, injection of chicken eggs with cephalosporins will no longer be allowed; the use of cephalosporins in feed will no longer be allowed; and the use of "bio-bullets" for cattle will no longer be sanctioned. Cephalosporins may still be use in "minor-food animals", such as bunnies and ducks. And previously approved veterinary uses are still allowable, such as the use of cephapirin (an older first generation ceaphalosporin, similar to cephalexin), which is commonly used as an intramammary infusion for mastitis in milk cows.

According to this article, the FDA attempted a similar ban in 2008, but was met with resistance for being overly broad. The current ban therefore does provide exceptions. *(A copy of the full FDA document can be found at http://www.gpo.gov/fdasys/pkg/FR-2012-01-06/pdf/2012-35.pdf.)* ■

Young girl survives rabies

Centers for Disease Control and Prevention. Recovery of a patient from clinical rabies – California, 2011. *MMWR* 2012; 61(4):61-65.

This report documents the fascinating story of an 8-year old girl from Humboldt County in northern California who survived rabies encephalitis last year. She is the 3rd individual in the United States without pre-exposure vaccination to have survived clinical rabies, and the second treated by therapeutic coma.

The clues to a speedy diagnosis in her case — essential to her survival —- included a lack of evidence of other compatible infectious illness or clinical syndrome, and the discovery of high risk animal exposure (she had contact with feral cats at her school 4 to 9 weeks earlier). Most importantly, although infectious encephalitis was suspected, the patient was experiencing severe bulbar dysfunction out of proportion to her other symptoms. The accompanying editorial points out that few causes of infectious

encephalitis other than rabies result in severe pharyngeal dysfunction.

The patient developed symptoms on April 25th and saw her pediatrician with sore throat and vomiting. Over the next few days, she developed progressive dysphagia. Three days later, she was see in the ER with dehydration requiring parenteral fluids. Over the next 2-3 days, she was brought back to the ER a second and third time with complaints of sore throat, dysphagia, weakness and abdominal pain. By the third visit, she was confused, tachycardic, and had WBC 19.2K. A head, abdomen and chest CT were attempted, but she choked on the oral contrast, developed respiratory distress and required intubation for airway protection. Her cerebrospinal fluid showed only 6 WBCs, a mildly elevated protein of 62 and a normal glucose of 67. The only other findings were left lower lobe atelectasis, a positive rhinovirus PCR, and a positive M pneumoniae IgM. Fortunately, based on her dysphagia, the diagnosis of rabies was suspected early, and she was treated with aggressive support and therapeutic coma. Rabies-specific virus antibodies were detected in CSF and blood on multiple occasions.

Contact investigation of 208 classmates found 2 with possible significant contact, both of whom received post-exposure prophylaxis. In addition, because of possible exposure to saliva, mucous membranes or open wounds, 8 family members, 3 pediatric ICU nurses at the referral hospital, and 14 health care personnel at the local ER received PEP.

The feral cats around her school were trapped and observed, none of which developed symptoms of rabies. She'd had no other suspect animal exposure, and no rabid bats were found on the family property. The MMWR report indicates that 303 rabid cats were reported in the United States in 2010 — including one cat with rabies from the same county as this child. ■

Should people with colds be in the NICU?

Miller EK, et al. Human rhinovirus in severe respiratory disease in very low birth weight infants. *Pediatrics* 2012; 129; e60 - 67.

Sometimes it's the most basic of questions that stops you short. I was recently contacted by L&D personnel regarding a 49 year-old ethnic Chinese woman, who presented for a twin delivery with pre-eclampsia. On admission she reported 3 days of cough, runny nose, chest congestion, and low-grade fever. She was dyspneic at rest, with obvious fluid overload, and a chest radiograph demonstrated interstitial infiltrates and bilateral pleural effusions. She was empirically treated with oseltamivir; EIA for Influenza A/B was negative and H1N1 PCR was pending. Two days later, the results of an oropharyngeal sample positive for human rhinovirus (HRV) was received. Pending that result, she had been allowed to be around the babies wearing a mask. Her chest xray improved but remained abnormal despite the administration of furosemide, although she was still grossly fluid overloaded from her eclampsia.

Unfortunately, one of the twins was moved to the NICU, and the question was could mom visit the baby in the NICU? Infection control policy does not allow anyone with a cough in the NICU, even with a mask, but one of the L&D staff protested — "Rhinovirus? Everyone has a cold in the winter," she said! "How can a cold be a problem?" Certainly mom was not happy, nor was the L&D staff.

Although generally thought of as causing the common cold, it is now recognized that HRVs are associated with lower respiratory tract infection, and can cause significant respiratory illness in infants and young children. Very low birth weight infants are especially at high risk for lower respiratory tract infection.

This study examined the viral etiologies of acute respiratory illness (ARI) during the first year of life in very low birth weight infants who had required initial NICU care. ARI was defined as one or more of the following symptoms: rhinorrhea, pharyngitis, cough, retractions, wheezing, or crackles, with or without fever. Bronchiolitis was defined as the acute onset of coryza, cough, chest retractions, tachypnea, and wheezing. Severe acute lung disease was defined as the need for rehospitalization, changes in oxygen requirements, and respiratory distress. Nasal wash specimens were tested by PCR for human rhinovirus (HRV), RSV, human parainfluenza virus, influenza virus, and human metapneumovirus.

Of 119 patients enrolled in the study, 303 episodes of ARI were identified, including 190 defined as bronchiolitis. Eighty-eight infants had a lower respiratory tract infection, 46 of whom had moderately severe to severe symptoms, and 33 infants required hospitalization. Of the 303 episodes, 41% were due to HRV, 7% to RSV, 4% to human parainfluenza virus type 3, 2% to human metapneumovirus, and 1% to human parainfluenza virus 1; there were 11 co-infections. Of those infants with bronchiolitis, 40% had HRV compared with 7% with RSV. HRV was associated with 12 (33%) of the hospitalizations compared with RSV (25%). The risk of HRV-associated hospitalization was highest for infants with a diagnosis of bronchopulmonary dysplasia and those who had not been breastfed. Surprisingly, HRV turned out to be the dominant respiratory pathogen in these low-birth weight infants during their first year of life — resulting in significant lower respiratory tract infection requiring rehospitalization in 10% of those studied. The common cold may be common but it is not to be sniffled at, especially for infants. ■

CME INSTRUCTIONS

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

1. Read and study the activity, using the provided references for further research.

2. Log on to www.cmecity.com to take a post-test; tests can be taken after each issue or collectively at the end of the semester. First-time users will have to register on the site using the 8-digit subscriber number printed on their mailing label, invoice or renewal notice.

3. Pass the online tests with a score of 100%; you will be allowed to answer the questions as many times as needed to achieve a score of 100%.

4. After successfully completing the last test of the semester, your browser will be automatically directed to the activity evaluation form, which you will submit online.

5. Once the completed evaluation is received, a credit letter will be e-mailed to you instantly.

CME QUESTIONS

1. Which of the following is correct?

A. The incidence of tuberculosis in the U.S. in 2011 decreased by 6.4% from the previous year.

B. The incidence of tuberculosis in the U.S. in 2011 increased by 6.4% from the previous year.

C. The incidence of tuberculosis in the U.S. Is decreasing at a rate indicating it will be eradicated by 2060.

D. The rate of tuberculosis is much higher in individuals born in the U.S. than in those born abroad.

2. Which of the following is correct?

A. In the U.S. In 2011, the greatest percentage decrease in incidence of tuberculosis was seen in individuals born in the U.S.

B. In the U.S. In 2010, the proportion of Mycobacterium tuberculosis isolates, among those for which susceptibility results were known, that were multi-drug resistant (MDR-TB) was 13%.

C. In the U.S. In 2010, the proportion of Mycobacterium tuberculosis isolates' among those for which susceptibility results were known, that were multi-drug resistant (MDR-TB) was 1.3%.

D. In the U.S. In 2010 , among Mycobacterium tuberculosis isolates for which susceptibility results were known, none were multi-drug resistant (MDR-TB) .

3. The syndrome and disease pattern referred to as dengue fever:

A. is rare in children under 10 years of age

B. is increasing in frequency

C. is most severe in previously unexposed individuals

without immunity

D. is acquired after nighttime bites by Anopheles mosquitoes

CME OBJECTIVES

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

- discuss the diagnosis and treatment of infectious diseases;
- explain current data regarding the use of new antibiotics for commonly diagnosed diseases and new uses for traditional drugs;
- discuss the latest information regarding risks, benefits, and cost-effectiveness of new and traditional diagnostic tests; and
- discuss new information regarding how infectious diseases are transmitted and how such information can lead to the development of new therapies.

[IN FUTURE ISSUES]

Gastrointestinal Basidiobolomycosis — An Emerging Disease

PCR and β-D-Glucan Assays for Diagnosing Invasive Candidiasis

Increased Risk for Retinal Detachment with Fluoroquinolones

PHARMACOLOGY WATCH

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

Does Aspirin Prevent Cancer?

In this issue: Aspirin and cancer prevention; rivaroxaban for pulmonary embolism; new rhinosinusitis practice guidelines; and FDA actions.

Is recommending aspirin next?

Should aspirin be recommended to prevent cancer? Many lines of evidence have suggested that regular low-dose aspirin reduces the risk of colorectal cancer. Can the inexpensive wonder drug reduce the risk of other cancers as well? Researchers in England led by Dr. Peter Rothwell recently published three meta-analyses that looked at aspirin use and long-term cancer incidence and metastasis, as well as the short-term effect on cancer incidence and mortality, and the effect of aspirin on cancer metastasis. More than 200 studies were included in the meta-analyses, which were initially done to assess aspirin's benefit on vascular disease. The three new studies used a combination of case-control, cohort, and randomized clinical trials.

In the long-term study, the 20-year risk of cancer death and metastases was evaluated whereas the short-term study looked at a 3-5 year time frame. The trial for prevention of metastatic disease included five large, randomized trials of daily aspirin vs control in patients who had new solid cancer diagnosed during the trial. In the long-term study, the odds ratio for colon cancer incidence was 0.62 in favor of aspirin, and the odds ratio was 0.58 for death from colon cancer in favor of aspirin. There were similar reductions in the rates of esophageal, gastric, biliary, and breast cancer. The rate of distant metastases was also reduced. The other two studies also showed reduced rates of cancer and reduced rates of metastatic disease.

In the short-term study, cancer rates were 24% lower with aspirin use at 3 years. Curiously, aspirin did not reduce the risk of vascular events but there was no increased risk of major bleeding, including intracranial hemorrhage.

In the meta-analysis of five trials looking at the rate of metastatic disease, a 36% reduction in cancer metastasis was noted, including a 46% reduction in metastatic adenocarcinoma (all three studies published online in *Lancet* and *Lancet Oncology* March 21, 2012.) An accompanying editorial points out that these studies show that aspirin at any dose reduces nonvascular deaths by 12% and cancer death by 15% with benefits seen within 3 years for higher doses (> 300 mg/day) and at 5 years for lower doses (< 300 mg/day). The major critique of the studies comes from the United States where the Women's Health Initiative Study and the Physicians' Health Study both failed to show benefit from aspirin on cancer mortality. Both of these studies used low-dose aspirin every other day, a dose that may be too low to show biological effect on cancer. Another critique suggests that aspirin may lead to earlier diagnosis of colorectal cancer since it may cause earlier gastrointestinal bleeding, explaining the lower mortality rate. Despite these concerns, the editorialists suggest that this "impressive collection of data moves us another step closer to broadening recommendations for aspirin use. Moreover, future evidence-based guidelines for aspirin prophylaxis can no longer consider the use

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of aspirin for the prevention of vascular disease in isolation from cancer prevention." (*Lancet* published online March 21, 2012). ■

Rivaroxaban for pulmonary embolism

Rivaroxaban, Janssen's oral factor Xa inhibitor, may be an effective alternative to heparin/warfarin for treatment of symptomatic pulmonary embolism, according to a new study. The drug is currently approved for the prevention of stroke in patients with nonvalvular atrial fibrillation and for deep vein thrombosis (DVT) prophylaxis following hip replacement. It has also been shown to be an effective treatment for DVT, although it is not approved for this indication. The new study was a randomized, open-label, event-driven, noninferiority trial comparing rivaroxaban to standard therapy with enoxaparin followed by adjusted-dose vitamin K antagonist for 3, 6, or 12 months for the treatment of pulmonary embolism. The primary outcome was symptomatic recurrent venous thromboembolism with a secondary safety outcome of clinically relevant nonmajor bleeding. In more than 4800 patients who were randomized, rivaroxaban was noninferior to standard therapy with 50 events in the rivaroxaban group (2.1%) vs 44 events in the standard therapy group (1.8%) (hazard ratio [HR], 1.12; confidence interval [CI] 0.75 to 1.68, noninferiority margin 2.0; $P = 0.003$). The principal safety outcome occurred in 10.3% of patients in the rivaroxaban group and 11.4% of those in the standard therapy group, while major bleeding occurred in 26 patients (1.1%) in the rivaroxaban group and 52 patients (2.2%) in the standard therapy group (HR 0.49; 95% CI, 0.31 to 0.79; $P = 0.003$). The authors conclude that a fixed-dose regimen of rivaroxaban was noninferior to standard therapy with enoxaparin and warfarin for the initial and long-term treatment of pulmonary embolism, and potentially showed an improved benefit-risk profile (*N Engl J Med* published online March 26, 2012). The doses of rivaroxaban used in the study were 15 mg twice a day for 3 weeks followed by 20 mg once daily for the duration. Rivaroxaban offers the advantage of oral therapy compared to enoxaparin and the lack of need for blood test monitoring compared to warfarin. ■

New practice guideline for rhinosinusitis

The Infectious Diseases Society of America has published its first Clinical Practice Guideline for Acute Bacterial Rhinosinusitis in Children and Adults. The guideline points out the difficulty in distinguishing bacterial vs viral sinus infections. The following are suggestive of bacterial infection: persistent symptoms of sinusitis lasting more than 10 days without evidence of improvement; onset of severe symptoms or signs with high fever, purulent discharge, or facial pain lasting at least 3-4 consecutive days; or onset with worsening symptoms or signs characterized by new onset of fever, headache, or increased nasal discharge following a viral URI. The guideline recommends empiric antibiotic therapy with amoxicillin-clavulanate rather than amoxicillin alone in both children and adults. Children should be treated for 10-14 days while adults should be treated for 5-7 days. The guideline further recommends beta-lactam agents for treatment of sinusitis rather than respiratory floroquinolones, macrolides, trimethoprim-sulfamethoxazole, or second- or third-generation oral cephalosporins due to emerging resistance patterns. Doxycycline may be used as an alternative. (*Clin Inf Dis* 2012;54:e72-e112. DOI: 10.1093/cid/cis370). ■

FDA actions

The FDA has approved the first new erythropoiesis-stimulating agent in more than 10 years. Peginesatide is approved to treat anemia associated with end-stage renal disease in patients on dialysis. The approval was based on two randomized, active-controlled, open-label trials which showed that the drug was as effective as epoetin in maintaining hemoglobin levels. The drug is not approved for chronic kidney disease patients who are not on dialysis or for cancer-related anemia. Peginesatide is marketed by Affymax Inc. as Omontys.

The FDA has approved the first generic ibandronate (Boniva), the popular once-monthly bisphosphonate to treat or prevent osteoporosis in postmenopausal women. Three companies have received approval to manufacture the drug including Apotex Inc., Orchid Healthcare, and Mylan Pharmaceuticals. The generic as well as the brand is dispensed with a medication guide regarding the possible risk of esophagitis, hypocalcemia, bone or muscle pain, osteonecrosis of the jaw, and atypical femoral fractures.

The FDA has also recently approved generic escitalopram (Lexapro), a selective serotonin reuptake inhibitor (SSRI) to treat adults with depression and generalized anxiety disorder. Teva Pharmaceuticals will be the first to market the generic in 5-, 10-, and 20-mg strengths. Like other SSRIs, escitalopram carries a box warning regarding increased risk of suicidal thinking and behavior in children, adolescents, and young adults. ■