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Infectious Disease [ALERT]

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

The 'No Name Virus' in the Land of 'Those Who Kill': Hantavirus in Yosemite

By Stan Deresinski, MD, FACP, FIDSA

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Prior to 2012, only 2 cases of hantavirus infection had been identified in visitors to California's Yosemite National Park – one in 2000 and another in 2010. Both infections were acquired in the Tuolomne Meadows area, miles distant from the iconic Yosemite Valley. Things changed this summer with 9 new cases identified as of September 13, only one of which was associated with visiting the High Sierra Camps of Tuolomne. The other 8 had stayed in the Curry Village area of the Yosemite Valley, all in "Signature Tent Cabins". These 91 relatively new cabins set off to one side of Curry Village have double-walls, which provides an element of insulation – but also presumably provides a site for rodent excreta to accumulate, while also possibly reducing ambient air exchange. Hantavirus, which may survive for as long as 13 days in the environment, would be protected from inactivating UV rays at this site.

The first case occurred in a visitor who stayed in Curry Village from June 10-12 and became ill on June 26. The Signature Tent Cabins were closed on August 28. Seven of the patients were residents of California, while one each was from Pennsylvania and West Virginia. Three of the 9 have died. Initial notifications were made in August to 30,000 visitors and on September 12th email notifications were sent to 230,000 overnight visitors. Approximately one-tenth of visitors are international and public health officials of 39 countries have also been notified of the outbreak and its consequences.

The hantaviruses, members of the Bunyaviridae, are a large family of >200 species of ssRNA negative strand viruses. All members of the Bunyaviridae such as LaCrosse virus, Rift Valley Fever virus, and Congo-Crimean Hemorrhagic Fever virus, are arboviruses – i.e., transmitted

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by arthropods. In contrast, those of the genus Hantavirus are primarily transmitted by inhalation of droplets with virus aerosolized from rodent feces and urine.

SIN NOMBRE

There are at least 11 hantaviruses associated with human disease manifested by two distinct syndromes. Species present in the Old World (e.g., Hantaan, Seoul, Puumula) typically cause hemorrhagic fever and renal syndrome (HFRS), while those in the New World cause hantavirus pulmonary syndrome (HPS) which, because of the frequent presence of myocardial depression, should more precisely probably be called hantavirus cardiopulmonary syndrome. HPS was first identified in the U.S. after an outbreak of illness in the region where the states of Utah, New Mexico, Arizona, and Colorado meet – the "four corners" which gave the virus its initial informal name. The official name first given to it was Muerto Canyon virus, but the local inhabitants strongly objected, fearing the besmirching of their region's reputation. As a consequence, the virus was renamed Sin Nombre – the "no name virus." Other hantaviruses that cause human infection in the U.S. include the New York, Bayou, and Black Creek Canal viruses. Each has its own rodent reservoir and geographic area.

The reservoir of the Sin Nombre virus is the deer mouse, a rodent that is present in most of the U.S.(excepting the eastern and southeastern coastal areas), as well as in the Alaskan panhandle, northern and western Canada, Baja and parts of Oaxaca, Mexico.

The usual incubation period is 10-17 days, but it has been reported to extend to as long as 6 weeks. The initial symptoms are non-specific, consisting of fever, chills, headache, nausea and vomiting. After several days, patients develop a non-productive cough. The development of breathlessness and tachypnea signal the onset of a rapidly progressive course with the development of acute respiratory distress syndrome (ARDS) and respiratory failure, as well as hypotension. The hypotension may be due to loss of intravascular volume due to capillary leak caused by effects of the virus on endothelial cells, as evidenced by low albumin and hemoconcentration, but is exacerbated by the frequent development of myocardial depression and cardiogenic shock.

Laboratory abnormalities that may be detected during the prodromal phase include thrombocytopenia, neutrophilia together with the presence of early forms including myelocytes, and immunoblasts. During the cardiopulmonary phase, chest x-ray is consistent with ARDS and there is evidence of impaired gas exchange that may become severe enough to necessitate mechanical ventilation. Renal function may be mildly depressed. Disseminated intravascular coagulation is uncommon. Echocardiography reveals depressed left ventricular function. In contrast to the usual findings in sepsis, hemodynamics are dominated by the cardiac abnormalities resulting in a low cardiac output and high systemic vascular resistance. Treatment is supportive since no antiviral agent, including ribavirin, has been demonstrated to be effective once HPS has developed. The diagnosis is made using antibody testing.
A total of 510 cases of HPS in the U.S. were reported from 30 mostly western states to the CDC from

1993 through 2009 and 35% of these were fatal.[1] Only 36% of cases occurred in females and only 7% in children <16 years of age. Until the current event, 60 cases of HPS had been reported in California since 1993 with 16 of these, 4 fatal, reported from 2001 through 2008. Eleven of these 16 infections were acquired in the Sierra Nevadas.

Ongoing investigations will determine the cause of this localized outbreak. While increased viral virulence as the result of mutation is possible, it is not likely to be the explanation. Instead, the outbreak may have result from a confluence of events, including an increase in the population of deer mice and the two-walled construction of the Signature cabins which, I speculate, may be more airtight than older cabins.
Hantavirus infection of deer mice in the Sierras is highly prevalent (14% are seropositive) and 13.7% trapped (using peanut butter as the lure) in Curry Village in August had antibody to Sin Nombre virus. While the localized nature of this summer's outbreak indicate a significant risk to visitors staying in Signature Cabins in Curry Village, identified human infections have been rare events when one considers that there were 4,098,648 visitors to Yosemite in 2011. It may nonetheless be considered ironic that the word Yosemite is derived from a Miwok word meaning "those who kill", referring to a group living in the valley composed of renegades from multiple tribes, including the Paiute who were traditional enemies of the Miwok. ■

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Is Doxycycline Protective Against the Development of *C. difficile* infection?

By Richard R. Watkins, MD, MS, FACP

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Dr. Watkins reports no financial relationships in this field of study.

SYNOPSIS: A historical cohort study from San Francisco General Hospital evaluated patients ≥18 years old that were hospitalized and received at least one dose of ceftriaxone. In a multivariable analysis, for every day a patient also received doxycycline the rate of *Clostridium difficile* infection was 27% lower than for those who did not receive doxycycline (hazard ratio, 0.73%; 95% confidence interval, 0.56-0.96).

SOURCE: Doernberg SB, et al. Does doxycycline protect against development of *Clostridium difficile* infection? *Clin Infect Dis* 2012;55:615-620.

Clostridium difficile infection (CDI) is a major complication associated with antibiotic usage, and its incidence continues to increase. Management of CDI remains challenging despite new therapies and many patients suffer from recurrences. Interventions to limit acquisition of the disease are therefore urgently needed. Not all antibiotics predispose to CDI equally, and there is some clinical evidence that certain antibiotics may be associated with a lower risk or even prevent it. Investigators sought to determine if doxycycline could avert CDI among patients who received ceftriaxone, a high-risk antibiotic. They performed a historical cohort study between June 1, 2005 and December 31, 2010 that included hospitalized patients ≥ 18 years of age who received at least one dose of ceftriaxone. Patients were excluded who were diagnosed with CDI in the 30 days prior to admission through 2 days after admission, or if diagnosed with CDI before they received ceftriaxone. The main outcome of interest was the onset of CDI within 30 days of initiation of ceftriaxone. The cohort consisted of 2,734 hospitalizations, with 2,305 different patients.
The results of the study were that 39% of patients (1,066) received doxycycline during their hospitalization, and 5 developed CDI for an incidence rate of 1.67 per 10,000 patient-days.

Of the patients who did not receive doxycycline, 38 developed CDI, an incidence rate of 8.11 per 10,000 patient days. Unadjusted analysis found white race to be associated with a 2.67-fold higher hazard of CDI compared with nonwhite race (95% confidence interval, 1.46-4.89; P = 0.001). There was a trend toward a protective effect with male gender (P = 0.06). On bivariate analysis, for every day of additional antibiotic receipt besides ceftriaxone, the hazard for acquiring CDI increased by 4%. For every day of doxycycline receipt the unadjusted hazard was 0.67-fold lower for developing CDI compared to patients not receiving doxycycline.

On multivariable analysis, for each additional day that a patient received doxycycline the rate of CDI was 27% lower compared to a patient not receiving it when adjusted for age, gender, race, comorbidities, duration of hospitalization, pneumonia diagnosis, surgical admission, and duration of ceftriaxone and other antibiotics. When a patient received a 5 day course of doxycycline the hazard for developing CDI was 0.21 fold that of a patient not receiving it when adjusted for other factors in the model (95% confidence interval, 0.05-0.82). The hazard ratio for developing CDI in a patient who received a 5 day course of doxycycline and ceftriaxone compared to a macrolide and ceftriaxone was 0.15 (95% confidence interval, 0.03-0.77), and was 0.13 compared to a 5 day course of a fluoroquinolones and ceftriaxone (95% confidence interval, 0.03-0.62). The strongest predictor of developing CDI was time spent in the hospital and the hazard for each day was 15.1 fold higher than for an outpatient.

The study had several limitations. First, all patients in the cohort were given ceftriaxone which would have increased their baseline risk for CDI. This made it difficult for the investigators to determine the increased risk of CDI specifically due to the duration of ceftriaxone. Second, trauma patients could have caused confounding of the results as they were commonly male and nonwhite, two groups shown in the study to have lower incidence of CDI. Third, measurement bias may have occurred since hospitalized patients who develop diarrhea are more likely to be tested for CDI than those who have been discharged. Fourth, antibiotics received before hospitalization were not recorded and could underestimate the subsequent risk for developing CDI. Finally, the authors did not identify the strain(s) of *C. difficile* present during the study.

COMMENTARY

Doxycycline plus a β-lactam antibiotic is an alternative recommendation for the treatment of patients hospitalized for community-acquired pneumonia (CAP) in the current IDSA/ATS guidelines.[1] The majority of patients with CAP admitted to the general floor at my hospital (which is similar in size to the authors') receive either levofloxacin or ceftriaxone plus azithromycin, while those admitted to the ICU receive levofloxacin or azithromycin plus ceftriaxone. The recent report on the cardiovascular risks associated with macrolides makes doxycycline look appealing.[2] It will be interesting to see if doxycycline usage in clinical practice increases in light of this study, especially for CAP. Furthermore, if doxycycline decreases the risk of developing CDI there would be even more reason to use it over macrolides and possibly quinolones, the latter of which carry a high risk for CDI.

The mechanism behind the possible protective effect of doxycycline is unknown. Several theories have been proposed, including its in vitro activity against anaerobic bacteria (including *C. difficile*), attenuating *C. difficile* toxin production, and the fact that doxycycline is mostly absorbed in the upper gastrointestinal tract which would spare the normal flora in the colon.[3,4] Tigecycline, a derivative of minocycline, has been used successfully in refractory cases of CDI.[5]

In the present study, patients who received doxycycline had shorter courses of antibiotics overall, which would intuitively decrease their risk for CDI. It was not randomized, which could predispose to confounding and uncertainty as to whether the observed association was due to the treatment or the type of patient to whom the treatment was administered. For instance, the cohort patients who received doxycycline were more likely to have had pneumonia on admission, less likely to have been admitted to a surgery service, had higher Charlson comorbidity indices, and received shorter courses

of additional antibiotics. Moreover, the authors did not determine whether patients in the cohort had an episode of CDI more than 30 days prior to hospitalization, as this may have led to increased risk. The incidence of CDI in this study was lower compared to prior studies. This might have been due to the enzyme immunoassay testing method used, which has poor sensitivity. Whether it impacted the results is uncertain. The incidence of CDI shows no sign of abating, and current infection control practices and antimicrobials are unlikely to curtail the epidemic. Novel and innovative solutions are required and will likely be the key to controlling the disease. Despite its limitations, this study has an important finding: hospitalized patients treated with ceftriaxone who also received doxycycline had a lower risk for developing CDI. Indeed, it could lead to adjustment of the paradigm for treating CAP by making doxycycline plus ceftriaxone first-line therapy. However, additional studies that verify the favorable association between CDI and doxycycline should be performed before changes to the current guidelines can be recommended. ■

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ABSTRACT & COMMENTARY

New phlebovirus associated with severe febrile illness in Missouri

By Dean L. Winslow, MD, FACP, FIDSA

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Dr. Winslow is a consultant for Siemens Diagnostic.

SYNOPSIS: Two men presented to a hospital in northwestern Missouri in June 2009 with fever, fatigue, diarrhea, thrombocytopenia and leukopenia. Both had a history of frequent recent tick bites. A novel phlebovirus was isolated in cell culture from patient blood. Electron microscopy revealed virus particles consistent with Bunyaviridae. Sequencing identified the viruses as novel members of the phlebovirus genus.

SOURCE: McMullan LK, et al. A new phlebovirus associated with severe febrile illness in Missouri. *New Eng Jrl Med* 2012;367:834-41.

Two men (one age 57 with no prior significant illnesses and one age 67 with type 2 diabetes) from northwestern Missouri presented separately to a hospital with illnesses characterized by fever, fatigue, diarrhea, thrombocytopenia and leukopenia. Hepatic transaminase levels subsequently became elevated in both patients, peaking between 8 and 10 days. Both reported frequent tick bites with most recent tick exposure 5-7 days prior to onset of illness. The patients were initially suspected of having ehrlichiosis and were given doxycycline pending diagnostic studies. Both patients eventually recovered from their illnesses but had symptoms of fatigue for as long as 2 years following their acute illnesses.

Blood samples sent to CDC were negative by PCR for Ehrlichia and rickettsiae of the spotted fever group. Subsequent serologic studies were negative for antibodies to spotted fever group rickettsiae and typhus. Leukocytes collected from the patients on day 2 of hospitalization were inoculated into DH82 cells and showed cytopathic effect, which was transferable to fresh DH82 cells. Electron microscopy revealed enveloped particles averaging 86 nm in diameter, typical of a virus in the Bunyaviridae family.

RNA isolated from infected cell cultures was sequenced using next-generation sequencing and was found to be similar to phleboviruses in the Bunyaviridae family. Sequences from the two patients were similar, but not identical, suggesting that the two patients were infected independently. Phylogenetic analysis showed clustering of these two new viruses with other tickborne viruses most closely related to severe fever with thrombocytopenia syndrome virus (SFTSV). Viral RNA of the novel virus was also detected in bone marrow from the second patient. Both patients demonstrated IgG antibody to the novel virus by ELISA more than 2 years following their acute illnesses.

■ COMMENTARY

One of the main reasons I decided to become an infectious diseases specialist when I was doing my Medicine residency during the 1970's was because I really enjoyed the challenge of trying to figure out what was wrong with very sick (usually febrile) patients. It was also during my internship that I cared for a patient with severe multi-lobar pneumonia who had recently attended a convention of the American Legion at the Bellevue-Stratford hotel in Philadelphia (about 2 years later the CDC finally identified the etiologic agent *Legionella pneumophila*). The next year I cared for a 14 year old girl who developed a faint sunburn-like rash, fever, and multi-system organ failure shortly after beginning to use a newly-marketed super-absorbent tampon (vaginal culture did grow *Staphylococcus aureus*, and a few months later other cases of menstrual TSS were identified in the U.S.). At the end of my fellowship training, Mike Gottlieb in Los Angeles described the first cases of Pneumocystis pneumonia in young gay men and we knew we were dealing with another new infectious disease (AIDS). During my career, the identification of new syndromes and newly-recognized etiologic agents of disease has continued with great regularity (Hantavirus pulmonary syndrome, SARS, pandemic H1N1 and many others come to mind).

This is an interesting case report which while not completely fulfilling Koch's postulates, almost certainly represents a newly-recognized tick-borne viral infection in North America. Many of the clinical and laboratory manifestations of this illness are similar to the also recently described SFTS bunyavirus illness seen in China.[1] Although the two patients described in the case report had severe illness, the spectrum of disease and extent of subclinical infection associated with this newly recognized phlebovirus is unknown. Also, while it is most likely that the common tick, *Amblyomma americanum*, is the vector for this virus, limited sampling of ticks in Missouri did not reveal the virus.

Coincidentally, Toscana virus (another phlebovirus originally isolated in 1971 in Tuscany) was recently shown to be responsible for 15% of cases of aseptic meningitis between July and October in northern Italy.[2] Since this latter virus has been recognized previously as a common cause of aseptic meningitis in the Mediterranean basin, its recognition recently in northern Italy may be a reflection of changing ecology related to global climate change. ■

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ABSTRACT & COMMENTARY

Thalidomide for IRIS? Optimal dose, duration unclear

By Dean L. Winslow, MD, FACP, FIDSA

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Dr. Winslow is a consultant for Siemens Diagnostic.

SYNOPSIS: A case series of three patients with severe immune reconstitution inflammatory syndrome (IRIS) was presented (2 associated with cryptococcal meningitis, 1 with tuberculosis) where patients developed IRIS which recurred following discontinuation or tapering of glucocorticoid therapy. Remission of IRIS was sustained by treatment

with thalidomide, allowing glucocorticoids to be tapered and discontinued.

SOURCE: Brunel AS, et al. Thalidomide for steroid-dependent immune reconstitution inflammatory syndromes during AIDS. *AIDS* 2012; 26: (epub ahead of print).

Three HIV-infected patients with refractory, corticosteroid-dependent and life-threatening IRIS were presented. The first patient with an initial CD4+ count of 15 cells/uL presented with cryptococcal meningitis which initially favorably responded to antifungal therapy and had HAART introduced on day 28.17 months later the patient presented with signs and symptoms of meningitis and cerebellar ataxia despite fluconazole suppressive treatment. At that time his CD4+ count was 273 cells/uL and his plasma HIV RNA was undetectable.

Lumbar puncture revealed raised intracranial pressure and was sterile on culture. MRI of the brain revealed bilateral cerebellar intensities on fluid-attenuation inversion recovery (FLAIR) images. The patient was initially managed with aggressive doses of IV methylprednisolone followed by oral prednisolone and increase in fluconazole to 800 mg/day. The patient experienced 3 additional relapses characterized by headache and diplopia when his predisolone was tapered to 12.5-15 mg/day. Thalidomide instituted in August 2010 at 100 mg/day and ASA 81 mg/day allowed complete cessation of steroids by March 2012.

The second patient also had cryptococcal meningitis and had an initial CD4+ count of 19 cells/uL, had a good initial response to antifungal therapy, HAART was initiated on day 21 and the patient continued to receive suppressive PO fluconazole. Two years later he was admitted with an encephalitis-like picture and his CD4+ count had risen to 353 cells/uL. MRI showed right parietal-temporal hyperintensity in FLAIR images and T1-weighted subarachnoid space enhancement after gadolinium administration. In this case as well, aggressive IV followed by PO glucocorticoid therapy was initiated along with continued fluconazole. When steroid therapy was interrupted the patient developed relapse of his symptoms in approximately 5 months followed by 2 additional relapses when steroids were tapered below 15 mg/day. Thalidomide and ASA were started in December 2010 and prednisone was stopped in June 2011. Thalidomide was finally stopped in March 2012 with no relapse to date.

The third patient had disseminated TB and a CD4+ count of 15 cells/uL at time of diagnosis. Antimycobacterial therapy was started and her HAART was optimized. Seven months later she was admitted to the hospital with abdominal pain and acute kidney injury. At that time her CD4+ count had risen to 104 cells/uL. MRI of the abdomen showed a voluminous mass encircling the mesenteric vessels and renal biopsy showed granulomas without caseous necrosis and negative AFB cultures. Glucocorticoids were administered along with continued anti-TB therapy with resolution of her symptoms. However the patient presented with 2 relapses of IRIS when the prednisone was tapered to 20 mg/day at 4 months and when interrupted at 23 months. Thalidomide, prednisone, and ASA were instituted following the second IRIS relapse. Prednisone was stopped 10 months later and thalidomide was stopped 14 months later with no sign of relapse to date.

■ COMMENTARY

IRIS occurring after institution of HAART in patients with HIV is felt to be related to a switch from a TH2 to a TH1 immune response and can be associated with increased levels of IFN-gamma and TNF-alpha. Thalidomide has been shown to inhibit production of TNF-alpha in vitro and is commonly used to treat both "reversal reactions" and erthyma nodosum leprosorum, which likely represent immune phenomena similar to HIV IRIS. Currently, systemic glucocorticoids remain the mainstay of treatment for severe life-threatening IRIS as illustrated in the 3 case reports included in this series. Obviously the use of steroids over long periods of time is problematic in patients due to glucocorticoid-related side effects.

This small case series suggests that thalidomide may be useful as a steroid-sparing agent in HIV IRIS. However, in addition to the problems with teratogenicity associated with thalidomide, the optimal dose and duration of thalidomide to treat IRIS is not clear.

For example, its efficacy even in the cases presented in this report is not clearly established since the patients all received long courses of

glucocorticoids and it is possible that their IRIS may have eventually resolved whether or not thalidomide had been administered.

Although off-label use of thalidomide proved successful in this small case series, prospective, randomized controlled trials of thalidomide for IRIS should be conducted prior to the use of this agent routinely for this condition. ■

Adequacy of Rabies Post-exposure Prophylaxis

By Lin H. Chen, MD.

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

SYNOPSIS: Travelers who experience animal bites often also experience delays in obtaining post-exposure prophylaxis, especially delays in obtaining human rabies immune globulin [HRIG]. Some develop suboptimal post-vaccination rabies antibody titers. Pre-travel advice needs to address ways to avoid these potential risks for rabies after bites which occur while overseas.

SOURCE: Uwanyiligira M, et al. Rabies post-exposure prophylaxis in routine practice in view of the new centers for disease control and prevention and world health organization recommendations. *Clin Infect Dis* 2012 Jul;55(2):201-5.

Uwanyiligira et al retrospectively analyzed charts of all patients seen at the Travel Clinic of the University Hospital in Lausanne, Switzerland, for rabies post-exposure prophylaxis (PEP) between January 2005 and August 2011. The study identified 110 patients, including 90 travellers. Their median age was 34 years (range, 2–79 years), and 53% were women. Of the 90 travelers with possible rabies exposure overseas, 54 sought evaluation at their destination, but 36 waited to obtain medical care until after return to Switzerland. Those who waited to obtain medical care in Switzerland had a median delay of 10 days (range 0-481 days) whereas those who started rabies PEP overseas had a median delay of 0 days (range 0-14 days).

All those who waited to initiate PEP in Switzerland received HRIG, but only 7/50 (14%) who initiated PEP overseas received HRIG. The countries where travelers received HRIG were Tunisia, Algeria, Thailand, Vietnam, Indonesia, and Brazil. However, HRIG administration was inconsistent in these countries because many other patients did not receive it.

There were 11 patients who received pre-exposure prophylaxis (PrEP) and rapid fluorescent focus inhibition tests (RFFIT) were done in these patients after the 2 post-exposure doses. Their geometric mean titer was 18.2 IU/ml (range 5.4-33.9 IU/ml). For 85 of the nonimmune patients, serology was obtained between 21-29 days after the 4th dose of rabies PEP. Their geometric mean titer was 3.7 IU/ml (range 0.1-38 IU/ml). Six of 90 previously unvaccinated patients had titers <0.5 IU/ml.

■ COMMENTARY

The GeoSentinel Surveillance Network analysis of 23,509 ill travelers seen from January 1998–May 2005 found 1.4% of the records indicated animal injuries That required rabies PEP.[1] The highest risk for exposure was travel to Asia (67% of cases), with Thailand, India, Indonesia, China, Nepal and Vietnam being leading countries where exposure occurred.[1] Dogs were the main culprits (51%), followed by monkeys (21%) and cats (8%); the most common reason for travel was tourism.[1] Most of the cases involved short-term travel: 12% travelled for <7 days, 53% travelled for <28 days, and 85% for <3 months, and their median trip duration was 23 days.[1]

Similarly, another study of 139 patients treated for possible rabies exposure at the Rabies PEP Service in the Liverpool School of Tropical Medicine from 2000 to 2009 found Thailand and Turkey to be the most common countries of exposure (22.3% of cases each).[2] Dogs were also responsible for most bites (49.6%), and the majority of patients (63%) were aged 20-50 years.[2] Only 3 of 78 (3.8%) of those needing rabies immunoglobulin (RIG) per UK guidelines received it while overseas and only 11 more patients received RIG on return to the UK; delay in care was also documented.[2] Only 14 (10.1%) had received PrEP.[2]

Gautret et al reviewed 22 published rabies cases occurring travellers (tourists, expatriates and migrants) within the past decade, including 3 cases following short-term travel (≤2 weeks).[3] Their review determined that expatriates were better vaccinated than tourists (31% vs. 12%) before travel.[3] The risk of bite with potential rabies exposure is estimated at 0.4% of travelers per month of stay in a rabies-endemic country.[3]

A survey of German travel health advisors confirmed the emphasis on PrEP for expatriates where nearly all responders indicated that they would discuss the risk of rabies and preventive measures to long-term travelers and tourists planning to visit rural areas.[4] However, only 35-60% of the advisors would provide this information to travellers on package tours or visiting urban centers or to business travelers.[4] Clearly, improvement is needed in proper post-exposure management to persons who had PrEP as well as in reducing the inappropriate withholding of PEP in cases where treatment had been initially delayed.[4]

Uwanyilijira et al proposed measuring antibody levels on day 21 of the Essen PEP regimen to ascertain an adequate immune response. In an editorial, Wilde et al pointed out that few or no laboratories in rabies endemic countries can perform appropriate serology.[5] Furthermore, failure to obtain PEP frequently is due to high cost of rabies vaccine and HRIG. Therefore, reducing the amount of rabies vaccine needed would contribute to better follow through with PEP, along with reducing the duration to initiation of PEP.[5] They noted that modern high-quality equine rabies immune globulin produced in France, Thailand, China, and India are available in some rabies-endemic countries. This information is reassuring, though difficult in practice for travellers to determine the quality of the product they receive in endemic countries. Also, Uwanyilijira et al have shown the inconsistent use of rabies immune globulin in a number of countries.

This study has raised questions regarding adequacy of the reduced-dose Essen PEP with 4 doses of rabies vaccine, based on the suboptimal antibody levels (<0.5 IU/mL) in 6 of 90 patients (6.7%) following 4 doses. The authors have also identified the additional problems of delayed initiation of PEP in travelers who waited to obtain medical treatment after returning to Switzerland. Travellers should seek proper post-bite care as soon as possible and understand the importance of HRIG in addition to rabies vaccination.

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Infectious Disease [ALERT]

Updates

By Carol A. Kemper, MD, FACP

Travel for the Hajj

National Travel Health Network and Centre, September 2012; http://www.nathnac.org/fact-sheets/Hajj_Umrah.htm

Travel to the Middle East may have gotten less popular recently, but for those planning to travel for the annual pilgrimage to Makkah (Mecca) October 24-29, 2012, The National Travel Health Network has issued updated guidelines, as follows:

• **Meningococcal Vaccine:** While meningococcal vaccine has previously only been recommended, it is now required for all travelers age 2 years or older. Proof of vaccination against Meningococcal meningitidis ACW1354 is now required to obtain a visa. In addition, in order to reduce the carrier rate, the Saudi Arabian Ministry of Health plans to administer prophylactic antibacterials to all

those arriving from the Africa continent.

• **Polio:** For those traveling from the United States who received polio vaccination more than 10 years earlier, at least one dose of oral polio vaccine should be administered at least 6 weeks prior to departure (Tdap is preferred). In addition, the Saudi Arabian Ministry of Health requires that travelers from countries endemic for polio (India, Pakistan, Afghanistan, Chad, Nigeria, Angola, etc.), regardless of age or polio vaccination status, receive a dose of OPV at least 6 weeks prior to departure, and all such travelers will receive an additional dose on arrival to the country. Further, travelers coming from a country where there has been a case of imported polio within the past 12 months (e.g., China, Yemen, Mali, etc.) must show proof of OPV vaccination within at least 6 weeks in order to obtain a visa — and they also will be required to receive an additional dose on arriving in the country.

• **Influenza:** Annual influenza vaccination is recommended.

• **MMR:** Current vaccination is routinely recommended.

•**Hepatitis B Vaccine:** A common ritual for men participating in Hajj is to have their heads shaved. While licensed barbers are legally required to employ a fresh blade with each new customer, illegal street venders may not follow the law. It is therefore recommended that travelers consider HBV vaccination.

• **Malaria:** Malaria is not present in Makkah, although it is present in the southwestern areas of Saudi Arabia. Travelers planning to visit this more rural region should consider malaria prophylaxis.

• **Specific recommendations for women:** They also recommend that women should consider hormonal therapy to avoid having a menstrual cycle. ■

Banner Year for West Nile Virus in U.S.

ProMEDmail post. September 10 and 13, 2012; http://www.promedmail.org.

This year is proving to be a banner year for West Nile Virus infection in the United States. Thus far, a total of 2,636 WNV cases have been reported in the United States, including 1405 cases of neuroinvasive disease and 118 deaths. More than 70% of cases have been reported from 6 States, including Texas, South Dakota, Mississippi, Oklahoma, Louisiana, and Michigan. Many of these areas have previously not been a focus of WNV infection — and it's not clear why certain areas, such as Dallas should be especially affected this year. As of September 4th, the greatest number of cases have been reported from Texas, with 1013 cases, including 40 deaths. This represents a 50% increase in cases in just 2 weeks. These numbers reflect only those infections that are recognized and reported, and disproportionately represent the severe cases. Most people who become infected have no clinical symptoms.

Two factors may be contributing to this increase. Scientists at the North East Regional Climate Center, Cornell University, who track climate conditions, report this was the warmest spring ever – which may contribute to an increase in mosquito larvae.

In addition, some communities have attempted to cut back on spraying, due to concerns about more general pesticide applications. Spraying for West Nile Virus typically contains a variety of insecticides, including malathion, methoprenes, and synthetic pyrethroids resmethrin and sumithrin. Generalized spraying for WNV in our area with malathion has met with protest. In addition, it has been demonstrated that the great lobster die-off along the Long Island Sound in 1999 (which wiped out more than 90% of the local lobster population) was likely due to the use of methoprenes used in Spraying of New York City that year to combat WNV. Methoprenes have been shown to function as an arthropod juvenile growth hormone agonist, promoting larval insect molting and changes in chitoproteins. Unfortunately, lobsters are also arthropods, and ground water run-off into the ocean containing this insecticide can result in small poorly formed lobsters, often with deformed shells. Similar small lobsters with deformed shells have been reported off the coast of Connecticut this year, probably for similar reasons. The New York House of Representatives just passed a bill in June 2012 banning the use of methoprene as an insecticide.

Alternatives include removing all standing water, empty all containers, bird baths or other

pools, and drain ponds and ditches, as well as avoiding mosquito bites, using screens on windows, protective clothing and mosquito deterrents. ■

HIV quickly invades the CNS

Valcour, et al. Central nervous system viral invasion and inflammation during acute HIV infection. *J Infect Dis* 2012; Advance publication June 11, 2012.

Twenty individuals with acute onset HIV infection underwent intensive neurologic evaluation, including comprehensive examination and laboratory study, cerebrospinal fluid examination, MRI and Magnetic resonance spectroscopy. One patient with acute syphilis and a high CSF white blood cell count was excluded. The average time from exposure to detection of infection was estimated to be 14.5 days (range, 4-31 days). The median CD4 count was 384 cells/mm3 (range, 218-740 cells/mm3). Headache was the only clinical complaint (in 11/20 subjects), and none had focal neurologic complaints or physical exam findings.

Lumbar puncture was performed in 18 participants (2 declined) a median of 17 days following estimated exposure. HIV RNA was identified in CSF in 15 subjects, at the earliest date of 8 days following exposure. CSF HIV RNA was negative in a single participant who underwent CSF sampling earlier than this at 4 days following exposure; this person's plasma HIV RNA was 2,231 copies/mL. Two other individuals had negative CSF HIV RNA testing, including one patient at 10 days following exposure (the plasma HIV RNA was 285,651 copies/mL; and another patient at 18 days following exposure (plasma HIV RNA 81,978 copies/mL.

The CSF HIV RNA level appeared to correlate with the plasma HIV level ($p < 0.007$), and was on average 2.4 log copies/mL lower than in plasma ($p < .001$). None of the patients had a CSF HIV RNA level higher than that found in plasma level (11 specimens were sampled on the same day). CSF neopterin levels were also elevated and correlated with plasma HIV RNA levels, and intrathecal immune activation was evident in 5 of 18 subjects. No structural abnormalities were identified on MRI. On MRS, there was a trend toward increased choline/creatine levels in the basal ganglia and occipital grey matter in individuals with acute HIV infection compared with those with chronic HIV disease or uninfected controls. The authors observed an association between higher neopterin levels and elevated choline/creatine levels, especially in the posterior cingulate gyrus.

Invasion of the CNS occurs early in the course of HIV infection (as early as 8 days), resulting in disturbances of inflammatory and metabolic markers, especially in the front lobes and cingulate cyrus, although did not result in any significant clinical findings other than headache. CSF HIV RNA levels generally parallel plasma HIV RNA. ■

This Piggie went to the Fair…

ProMEDmail post September 11, 2012; http://www.promedmail.org.

Of course, I happened to be visiting Minnesota and planned to attend the State Fair the weekend before Labor Day, just as health alerts reported the first cases of "swine flu" in humans associated with the Fair. For those of you not in the know – the Minnesota State Fair is a huge affair, covers several acres with extensive animal barns, and goes on for 12 days, including Labor Day Weekend. More than 1.7 million people attend the Fair yearly – typically 120,000-130,000 per day. And this news did not keep them away.

A total of 4 cases of this new "swine flu" have thus far been confirmed, all of which occurred in children and teens who spent long hours in the swine barn (the kids basically spend the entire day working with their animals and hanging out in the stalls and corridors with friends). The most recent case was identified in a teenage boy who was exhibiting hogs between August 23-26, and became ill 4 days later after going home. All 4 individuals quickly recovered with no sequelae. There has been no evidence of human-to-human transmission with this virus. The Minnesota Department of Health indicates that 2 sick pigs at the fair have also tested positive for H1N2v. The virus has been identified as a variant H1N2 Influenza A virus (H1N2v). Interestingly, it carriers the matrix gene from the 2009 H1N1 pandemic virus, which suggests that it could potentially be transmissible

in humans. Ongoing surveillance by the Department of Agriculture has identified other similar influenza viruses in pigs in Minnesota and other states as early as 2010, some containing the matrix gene, although none had previously caused human disease. Other H1N2 viruses have rarely caused disease in humans, typically in children or teens with close contact with animals.

This H1N2v "swine flu" strain is different from the other new strain of influenza, H3N2v (aren't all these new strains "v" by definition ?), that has resulted in 297 cases in the Midwest, also linked to agricultural fairs. This strain also carries the 2009 H1N1 matrix gene, and while human-to-human transmission with this virus has not been confirmed, the CDC suggests there have been cases where human transmission was suspected. ■

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 with regard to hantaviruses?

A. They are single strand DNA viruses.
B. Most, but not all, are transmitted by arthropods.
C. In Europe the lungs are an important target organ while in the U.S. the kidneys are a major target of disease.
D. They are members of the Bunyaviridae

2. Which of the following is correct with regard to infections with the Sin Nombre virus?

A. It is transmitted by arthropod bites.
B. Human-to-human transmission is frequently been observed.
C. Its reservoir is the deer mouse.
D. Its usual incubation period is 3-5 days.

3. Which of the following is correct with regard to the phlebovirus infections newly described by McMullen and colleagues?

A. Both patients had had tick bites.
B. They occurred in rural Washington state.
C. The viruses were members of the Bunyaviridae
D. The cases were rapidly fatal.

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]

Special report: Antibiotic Stewardship

Multicenter study: Post-prescription review, feedback cuts antimicrobial use

Unnecessary use of IV fluoroquinolones in acute care wards

Clinical Briefs in Primary Care™

The essential monthly primary care update

By Louis Kuritzky, MD

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

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Refining the Relationship Between Thyroid Hormones and Left Ventricular Mass

Source: Iida M, et al. *J Am Soc Hypertens* 2012;6:261-269.

Animal studies have shown that thyroid hormones (T3 and T4) induce hypertrophy of cardiac myocytes through stimulation of both structural and regulatory myocyte genes, which can be prevented by ACE inhibitors or beta-blockers. Such observations have led to the question of whether there might be a relationship between cardiac mass and thyroid hormones, even within the range currently defined as normal.

Hypothyroidism and hyperthyroidism are each considered a potential secondary cause of hypertension: the former through endothelial dysfunction that leads to vasoconstrictor hyperresponsiveness and subsequent increased peripheral resistance, and the latter through increased sympathetic tone. Iida et al investigated hypertensive subjects (n = 293) who had no known thyroid disease and whose thyroid function tests (T3, T4, and TSH) were within normal limits.

Among these euthyroid hypertensive study subjects, multiple linear regression found a positive relationship between T3 and T4 and ventricular mass (the higher the thyroid hormones, the greater the ventricular mass), and an inverse relationship between TSH and ventricular mass. When compared with normotensive controls, no such relationship could be identified. This would lead to consideration that in persons with hypertension, higher levels of thyroid hormone — even within the normal range — may be related to the development of left ventricular hypertrophy. ■

The ORIGIN Trial: Basal Insulin vs Standard Care for Early Type 2 Diabetes

Source: The ORIGIN Trial Investigators. *N Engl J Med* 2012;367:319-328.

Type 2 diabetes reflects insulin insufficiency. Early in the disease process, plasma insulin levels may actually be higher than normal, but insufficient to maintain euglycemia. By the time of formal diagnosis, approximately half of beta cell mass has been lost, and as the disease progresses, insulin levels continue to fall.

The Outcome Reduction with an Initial Glargine Intervention (ORIGIN) trial randomized subjects with prediabetes or early diabetes (n = 12,537) to insulin glargine (GLAR) or standard treatment (STND) for 6.2 years (mean). The objective of the trial was to determine whether early institution of basal insulin, as compared to STND, improves cardiovascular outcomes. Standard treatment was simply treatment of diabetes as per the treating clinician's choice; by the end of the trial, only 11% of the STND group was receiving insulin. Eighty percent of the GLAR group was on insulin at the end of the trial.

There was no difference in cardiovascular outcomes between the two treatment groups. One notable difference between treatments was the likelihood of progression from prediabetes to diabetes. The GLAR group was 28% less likely to progress than the STND group; however, there was also more hypoglycemia and weight gain in the GLAR group.

Increased incidence of cancer — a concern generated by earlier insulin trial data — was *not* seen in this large trial, and hence should be very reassuring. ■

Bronchodilators in COPD and Arrhythmias

Source: Wilchesky M, et al. *Chest* 2012; 142:298-304.

For chronic obstructive pulmonary disease (COPD), except for the provision of oxygen in late-stage disease, no pharmacologic intervention has been confirmed to save lives. Nonetheless, since bronchodilators improve symptoms, quality of life, and exercise capacity, and reduce acute exacerbations of COPD, they play an important role in routine care. Concerns about the potential capacity for arrhythmogenicity of bronchodilators has arisen from clinical COPD trials such as the Lung Health Study (n = 5887), in which short-acting ipratropium bromide was associated with a three-fold greater incidence of arrhythmia than comparator groups. Other smaller trials have not confirmed these findings, hence clarification is needed.

Wilchesky et al analyzed data from the province of Saskatchewan, Canada, to identify COPD subjects (n = 6018) and compare the incidence of arrhythmia in new users of ipratropium, beta-agonists (short- and long-acting), and methyhlxanthines to non-users.

Short-acting anticholinergics were

associated with a 2.4 relative risk of arrhythmia, and long-acting beta-agonists with a 4.5 relative risk. No statistically significant increased risk was seen with short-acting beta-agonists or methylxanthines. Despite these concerns, the authors remind us that the absolute risk increase was very small, and "in most cases would be outweighed by the therapeutic benefit accrued through symptomatic relief and consequent improvements to quality of life." ■

Reversible Dementia from Corticosteroid Therapy

Source: Cipriani G, et al. *Clin Geriatrics* 2012;20:38-41.

Although there are many clinical situations in which corticosteroids (CTS) are disease modifying and life saving, one aspect of CTS that has not received much attention is the potential for central nervous system (CNS) adverse effects. CTS may be largely subgrouped into mineralocorticoids exemplified by aldosterone, and glucocorticoids (GLC) like prednisone, the latter of which is the object of this case report.

There are at least two types of CTS receptors in the brain: type I (mineralocorticoid receptors) and type II (glucocorticoid receptors). Type II receptors are found in the hippocampus as well as diffuse other sites throughout the brain. The hippocampus is required for voluntary recollection of learned information, such as recalling what you had for dinner last night. Even low doses of GLC have been shown to impair hippocampal function, despite being used for short time periods: doses of prednisone of 80 mg/day have been shown to alter cognitive function within 4-5 days.

The authors include discussion of a report detailing six cases of dementia-like cognitive decline (distinct from steroid psychosis) in patients whose cognitive function was restored upon GLC discontinuation.

Clinicians should be vigilant for decline in cognitive function in persons receiving GLC treatment, even over the short-term. ■

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Could Thinner be Worse for Newly Diagnosed Diabetics?

Source: Carnethon MR, et al. *JAMA* 2012;308:581-590.

Usually, we anticipate a direct relationship between overweight and cardiovascular adversity, attributed to increases in blood pressure, lipids, glucose, insulin resistance, and sympathetic tone that are associated with obesity. There appears to be some exception to this general rule in reference to diabetes. For instance, in the TRIAD study, diabetics who were normal weight at entry to the study had a *higher* mortality than overweight/obese study subjects; similarly, in the PROactive trial, normal weight subjects or those who lost weight had *higher* mortality than overweight subjects. Because these two studies included confounding issues such as diabetes of varying duration and pre-existing cardiovascular disease, a more clear-cut relationship between body mass index (BMI) and outcome in diabetes could be discerned by selecting newly diagnosed diabetics.

Carnethon et al performed a pooled analysis of five longitudinal cohort studies (n = 2625) to examine the relationship between mortality and BMI for persons with newly diagnosed diabetes. Overall, only 12% of study subjects had a BMI < 25 at the time of diagnosis, but the relative risk for total mortality during follow-up (up to 15 years) was essentially doubled in this population compared to overweight individuals.

The mechanism(s) by which lower BMI increases mortality risk are unknown. Clinicians must not be falsely reassured that this lower-BMI phenotype, which is commonly seen in Asian-Americans, portends a favorable future. ■

The Impact of Exercise on Depression in Heart Failure

Source: Blumenthal JA, et al. *JAMA* 2012;308:465-474.

It is estimated that 5 million Americans have chronic heart failure (CHF), and almost half of these patients fulfill diagnostic criteria for depression. Subsyndromal depression is present in as many as 75%. Notwithstanding the burden of depression on quality of life, a direct impact on mortality has been shown in post-myocardial infarction patients, and even in patients with hypertension in the Systolic Hypertension in the Elderly Program. Unfortunately, to date the information on the impact of treating depression is both limited and generally disappointing. For instance, a clinical trial of sertraline in depressed patients with CHF found no cardiovascular event outcomes benefit.

Exercise is a treatment for depression, and exercise has been shown to provide event reduction in CHF patients. Whether it might improve depression and cardiovascular events in CHF patients was the object of the HF-ACTION trial (Heart Failure-A Controlled Trial Investigating Outcomes of Exercise Training).

More than 2000 patients with stable CHF were randomized to an aerobic exercise program. The exercise subjects enjoyed a statistically significant 11% reduction in mortality over the next 30 months. Although the mean score on the Beck Depression Inventory was statistically significantly lower in the exercise group, the improvement was sufficiently modest to be of uncertain clinical impact. Exercise in CHF reduces mortality and may have a modest effect on depression. ■

PHARMACOLOGY WATCH

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

Statins and Cognition — More to the Story?

In this issue: Side effects of statins; effects of cannabis use; antihypertensives and lip cancer; and FDA actions.

Review challenges FDA warning

Do statins cause changes in cognition? In February, the FDA added warnings to statin labels regarding the risk of reversible memory loss and confusion. But a new review from the *Journal of the American College of Cardiology* reviews the evidence given to the FDA and concludes "that there is no increased risk of cognitive decline" with statin use. The State-of-the-Art Paper was a comprehensive review of case reports, observational research, and randomized, controlled trials of statins and cognitive change, as well as risk of cancer and diabetes. Most of the evidence for cognitive changes came from individual case reports, many of which were self-reported by consumers to the FDA. Observational studies gave mixed results on cognition with four of nine studies showing statins improved cognition, while three showed no change, and two studies found an increased risk of cognitive impairment. The authors suggest that these studies are inconclusive and prone to selection bias. Two large, randomized, controlled clinical trials specifically looked at the effect of statins on cognitive function as the major secondary endpoint. In both, no significant differences were seen between the study and control groups with regard to cognitive decline. Twelve smaller studies showed mixed results with the majority showing no change and only one in 12 showing a detrimental effect of statins on cognitive function, while two studies showed a benefit. Along with lack of evidence to suggest statins lead to cognitive decline, the authors also found no evidence that statins increase the risk of cancer. They did, however, find a small risk for development of diabetes, which they felt was "outweighed by the cardiovascular benefits in patients for whom statin therapy is recommended" (*J Am Coll Cardiol* published online August 15, 2012). ■

Cannabis use and cognitive decline

Persistent cannabis use — particularly in adolescence — may lead to permanent cognitive decline, according to a new study. Researchers looked at a birth cohort of 1037 healthy individuals in New Zealand who underwent neuropsychological testing in the mid 1980s before the onset of cannabis use, and then again in 2010-2012 after some had developed a persistent pattern of cannabis use. Persistent cannabis use over 20 years (at least 4 days per week) was associated with neuropsychological decline, with greater decline evidence for more persistent users. This effect was only seen in adolescent-onset cannabis users and was associated with an average 8 point loss in IQ by age 38. The effect persisted after controlling for education, other drugs, or tobacco. The effects were not seen among adult-onset cannabis users. The authors conclude that increasing efforts should be directed toward delaying the onset of cannabis use by young people, "particularly given the recent trend of younger ages of cannabis use initiation in the United States and

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evidence that fewer adolescents believe that cannabis use is associated with serious health risk." (*Proc Natl Acad Sci U S A* published online August 27, 2012). This study and others are increasingly important as cannabis, the most widely used illicit drug in the world, is being considered for more medicinal uses as well as legalization. ■

Antihypertensives and lip cancer

Two photosensitizing antihypertensives, hydrochlorothiazide and nifedipine, may increase the risk for lip cancer in non-Hispanic white patients, according to a new study from Kaiser Permanente in California. From a large cohort of patients, 712 were identified with lip cancer along with nearly 23,000 matched controls. At least a 5-year supply of the drug resulted in the following odds ratios for lip cancer (95% confidence intervals) — hydrochlorothiazide 4.22 (2.82-6.31), hydrochlorothiazide-triamterene 2.82 (1.74-4.55), nifedipine 2.50 (1.29-4.84), and lisinopril 1.42 (0.95-2.13). When atenolol was given without other hypertensives, the odds ratio for lip cancer was 0.54 (0.07-4.08). The authors suggest that while antihypertensive therapy outweighs the risk of lip cancer, preventive measures should be taken for those at increased risk because of fair skin and long-term sun exposure (*Arch Intern Med* published online August 06, 2012). ■

FDA actions

The FDA has approved a delayed-release form of prednisone for the treatment of endocrine, inflammatory, and neoplastic conditions. Delayed-release prednisone should be taken once a day with timing to be determined by the disease being treated. For example, 10 p.m. dosing is recommended for rheumatoid arthritis, as it is more effective than immediate-release prednisone taken in the morning for treating morning stiffness associated with the disease. Dosing is based on the theory that both cytokines and endogenous cortisol follow a circadian rhythm, and that dosing the drug based on the condition being treated may afford more effective treatment than immediate-release prednisone. The new product delays the release of prednisone by approximately 4 hours. Side effects are the same as short-acting prednisone. Delayed-release prednisone will be marketed as RAYOS by Horizon Pharma.

The FDA has approved a new chlorofluorocarbon (CFC)-free, over-the-counter inhaled racepinephrine product for the treatment of asthma. The new product takes the place of the banned Primatene Mist, which was taken off the market at the end of 2011 because it contained CFCs. Inhaled epinephrine has been used for the treatment of asthma for more than 100 years. Marketed as Asthmanefrin, the new product will be sold as a starter kit and refill package. The starter kit will include 10 vials of racepinephrine along with the EZ Breathe Atomizer. The refill kit will include 30 vials of the drug. The drug is not without controversy, however, with many asthma experts feeling that the side effects of epinephrine are serious and well-documented, and over-the-counter use goes against published guidelines for treating asthma. Asthmanefrin will be marketed by Nephron Pharmaceuticals.

The FDA has approved linaclotide for the treatment of chronic idiopathic constipation and irritable bowel syndrome with constipation. The drug is the first guanylate cyclase (GC-C) agonist that acts locally in the gut with minimal systemic exposure. The drug is taken once daily on an empty stomach at least 30 minutes before the first meal of the day. Safety and efficacy in the management of irritable bowel syndrome with constipation was established in two double-blind studies of nearly 1300 patients who were randomly assigned to linaclotide or placebo for 12 weeks. Patients taking the drug experienced more complete spontaneous bowel movements than those taking placebo. The drug should not be used in patients 17 years or younger. Linaclotide will be jointly marketed by Ironwood Pharmaceuticals and Forest Pharmaceuticals as Linzess.

Montelukast (Singulair), Merck's popular asthma and allergy medication, will soon be available as a generic. The leukotriene receptor antagonist will be manufactured by 10 generic companies in tablet form, oral granules, and chewable tablets. The FDA warns that montelukast should not be used for relief of sudden asthma attacks and further warns that patients should contact a clinic immediately if they are experiencing behavior and mood-related changes such as aggression, depression, or hallucinations.

The FDA has approved the first generic version of pioglitazone (Actos). The drug is approved along with diet and exercise to improve blood sugar control in adults with type 2 diabetes. This happens as thiazolidinediones have generally fallen out of favor for use in type 2 diabetes due to side effects including worsening heart failure and edema. The FDA also recently issued a warning for pioglitazone regarding increased risk of bladder cancer if the drug is taken for more than 1 year. The first generic pioglitazone will be manufactured by Mylan Pharmaceuticals. ■