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ABSTRACT & COMMENTARY

Infections Associated With Travel *to* the United States

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

SYNOPSIS: Infectious illness is common in travelers from other countries visiting the United States. Skin and soft tissue infections, respiratory infections, and gastrointestinal illness are most likely, but specific geographic illnesses such as Lyme disease also occur.

SOURCE: Stoney RJ, Esposito DH, Kozarsky P, et al. Infectious diseases acquired by international travelers visiting the USA. *J Travel Med* 2018;25:1-7.

Typically, travel medicine specialists are concerned with health risks to travelers leaving a home in a "developed" country and traveling to a low-resource country. However, nine of the top 10 international tourist destinations are in North America or Europe; the United States reported more than 77 million visits by international tourists in 2015 alone. Infections in travelers to the United States have not been studied extensively. Therefore, researchers participating in the GeoSentinel Network reviewed data about all nonmigrant, non-U.S.-resident international travelers who experienced an illness during or soon after a trip to the United States and who sought care in a GeoSentinel Network clinic from January 1997 through December 2016. The GeoSentinel Network includes 70 participating travel and tropical medicine clinics in 30 different countries and was created in 1995 as a collaboration between the CDC and the International Society of Travel Medicine. Data-sharing allows for dissemination about outbreaks of illnesses and facilitates research about travel-related diseases.

During the study period, there were 1,393 relevant diagnoses made in 1,222 travelers. The sick travelers had come from 63 different countries (more than half from Canada or Europe). Of the ill travelers, 82% had been traveling as tourists, and the median duration of the trip was 14 days (range, one day to seven years). Overall, 52% of travelers were female,

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and 9% were < 18 years of age. A total of 177 patients were seen for an illness at a GeoSentinel site in the United States during their trip. Of the ill patients, 14% had skin and soft tissue infections, 7% had an acute gastrointestinal illness, and 7% had pneumonia. Sepsis, pyelonephritis, and influenza each were seen in 2% of ill travelers. Three travelers died while still in the United States (one with pneumonia and a subsequent cardiac event, one from pulmonary embolus, and one with cancer and pre-existing peritonitis who became septic).

The study included 1,045 travelers who sought care at a GeoSentinel site after the conclusion of the U.S. travel. Among them, insect bites/stings were common (15% of diagnoses), while flu-like illness (6%), upper respiratory infection (5%), acute gastrointestinal infection (4%), and skin and soft tissue infections (4%) also were seen. Influenza and Lyme disease each were diagnosed in 4% of returned travelers. There were nearly twice as many infections diagnosed in returned travelers during 2009 than in any other study year; this coincided with a global pandemic of influenza H1N1 infection.

In addition to Lyme disease, several other specific regional diseases were identified. There were 13 cases of coccidioidomycosis, mostly from Arizona. There was one case of Zika following travel in south Florida. There were three cases of dengue fever after travel in Florida and Hawaii. Two travelers acquired West Nile virus infection in the United States. Two travelers had spotted fever rickettsiosis, and one had ehrlichiosis.

■ COMMENTARY

Travel-related infections are not limited to visitors to resource-limited countries. We must abolish any residual notion of "us and them" where "we" are from clean countries and "they" are at risk in dirty countries. This paper serves as a good reminder that international visitors to the United States are at risk of infections during travel, and some of these infections could have been prevented with repellent use to reduce tick and mosquito bites. In addition, recent outbreaks of *Salmonella*,[1,2] *Campylobacter*,[1] norovirus,[2,3] *Escherichia coli*,[2,3] and *Cryptosporidium*[3] in the United States remind us that food, water, and hand hygiene still are important in the United States (a textbook about geographic infections is in its second edition and includes a 19-page chapter on infections in the United States).[4] Even as Americans are at risk of mosquito-borne diseases when visiting Africa, international travelers are at risk of various travel-related infections in the United States.

Perhaps it is helpful to review geographical illnesses in the United States, even beyond the current report in travelers. Specifically, the following states and regions have been linked with the noted infections: Hawaii (leptospirosis, dengue fever, *Angiostrongylus cantonensis*), Southwest (coccidioidomycosis), Texas (dengue fever, leprosy [with armadillo contact]), Midwest (Lyme disease, babesiosis), Florida (dengue fever, Zika, chikungunya), East-Central (histoplasmosis, blastomycosis), and Northeast (Lyme disease, babesiosis). This paper also provides a good reminder to all of us who live and travel within the United States. We should avail ourselves of annual influenza vaccines. We should clean injured skin carefully, avoid close contact with people who are actively coughing and sneezing, and use insect repellent on skin exposed in areas where dengue, Zika, and Lyme disease occur. Respiratory illnesses after visits to Arizona and California could prompt consideration of coccidioidomycosis. ■

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ABSTRACT & COMMENTARY

Prophylactic Antibiotics for Acute Aspiration

By Dean L. Winslow, MD, FACP, FIDSA

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

SYNOPSIS: Researchers compared outcomes in patients with aspiration pneumonitis who received prophylactic antibiotics during the first two days after macroaspiration to patients who received only supportive care during this time. Among 200 patients meeting the acute aspiration pneumonitis case definition, antimicrobial prophylaxis was not associated with improvement in mortality.

SOURCE: Dragan V, Wei L, Elligsen M, et al. Prophylactic antimicrobial therapy for acute aspiration pneumonitis. *Clin Infect Dis* 2018;67:513-518.

Dragan et al reported on a retrospective cohort study conducted in Toronto that included many patients. The authors evaluated outcomes for patients with aspiration pneumonitis who received prophylactic antibiotics compared to those who received supportive care only in the first two days after the observed aspiration event. The primary outcome was in-hospital 30-day mortality. The secondary outcomes were transfer to critical care, antimicrobial therapy received between days 3 and 14 after aspiration, escalation of antibiotic therapy, and antibiotic-free days.

Of 1,483 patient charts reviewed by investigators, 200 met the acute aspiration pneumonitis case definition. Thirty-eight percent received prophylactic antimicrobials and 62% received just supportive care in the first two days after the macroaspiration event. After investigators adjusted for patient-level predictors, they found that antimicrobial prophylaxis did not improve 30-day mortality or prevent transfer to the ICU. However, patients who received early prophylactic antimicrobials subsequently underwent antibiotic therapy escalation more often (8% vs. 1%; $P = 0.002$) and took antibiotics for fewer days (7.5 vs. 10.9; $P < 0.0001$).

■ COMMENTARY

During the last five years since I have been working full time at our university hospital and our excellent VA (where I receive my own medical care), I have been attending more on the inpatient medicine service than I have on the infectious disease consult service. I also have had the opportunity of seeing day-to-day clinical decision-making in a university hospital up close. Probably at least once each week, I'll overhear a resident sign out something to the effect: "Patient X vomited and aspirated last night, was a bit wheezy, so I covered him/her with vancomycin and piperacillin-tazobactam." I often challenge the residents by asking where they learned that "covering" patients after aspiration with broad-spectrum antibiotics is a good idea. The answer I often receive is, "This is standard of care." Additionally, a few days later, I'll hear them say, "Patient X has been on vancomycin and piperacillin-tazobactam for empiric coverage for aspiration for four days and his WBC went from 6,000 to 10,000 last night, so we empirically broadened coverage to meropenem." Again, I'll often challenge that decision, too. Now, I can forward a good paper to the house staff that I hope will reassure them that it is OK to withhold empiric antibiotics after aspiration. ■

ABSTRACT & COMMENTARY

Primary Headaches: Look, Listen, and Diagnose Rather Than Image

By Dara G. Jamieson, MD

Associate Professor of Clinical Neurology, Weill Cornell Medical College

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

SYNOPSIS: The diagnosis of primary headache disorders by a computerized and clinical paradigm can predict a baseline prevalence of intracranial abnormalities on brain imaging. Some historical "red flags" in children with headaches, including morning headaches and occipital pain, are not associated with increased intracranial abnormalities.

SOURCES: Wang R, Liu R, Dong Z, et al. Unnecessary neuroimaging for patients with primary headaches. *Headache* 2018; Aug 23. doi: 10.1111/head.13397. [Epub ahead of print].

Irwin SL, Gelfand AA. Occipital headaches and neuroimaging in children. *Curr Pain Headache Rep* 2018;22:59.

Tsze DS, Ochs JB, Gonzalez AE, Dayan PS. Red flag findings in children with headaches: Prevalence and association with emergency department neuroimaging. *Cephalalgia* 2018; Jan 1. doi: 10.1177/0333102418781814. [Epub ahead of print].

Brain imaging often is used to differentiate between primary headaches without specific neuroimaging correlates and secondary headaches due to visible brain lesions. However, the ubiquity of headaches necessitates a parsimonious approach to brain imaging. The study from Wang et al at the Headache Center of the Chinese People's Liberation Army General Hospital was designed to verify that primary headache patients do not need neuroimaging. Brain imaging was obtained in 1,070 healthy controls (345 male, aged 40.18 ± 12.46 years) and 1,070 primary headache patients (345 male, aged 40.05 ± 12.30 years) diagnosed by computerized clinical decision support systems (CDSS) and correlating clinical assessment. The CDSS is an interactive decision support system using computer software and International Classification of Headache Disorders criteria to diagnose based on clinical data.

The primary headache diagnosis, without "red flags" by history or abnormality on examination, was confirmed by a headache specialist. Primary headaches were migraine (62%), tension-type (32%), trigeminal autonomic cephalalgias (5%), and other (1.5%). In each group, 382 participants underwent CT scans and 688 underwent MRI scans based on individual non-neurological considerations. The neuroimaging findings were classified as significant abnormalities, nonsignificant abnormalities, or normal. Significant abnormalities were defined as neoplastic disease, hydrocephalus, vascular malformations (aneurysms, arteriovenous malformations, dural fistula, and/or cavernous angiomas), Chiari malformations, intracranial hemorrhages, and acute infarcts. White matter lesions, commonly seen in migraineurs, were not considered a significant finding. The rate of significant abnormalities, which were noted only on the MRI scans, was not significantly different in the primary headache group (four patients: two hydrocephalus, two nose/throat tumors) compared to the healthy controls (five controls: two cerebral infarction, one acoustic schwannoma, two cavernous angiomas). The authors concluded that with the possible exception of the very rare diagnosis of retinal migraine, neuroimaging is not necessary for patients with the presumed diagnosis of primary headaches.

Headaches in children are especially concerning to physicians and parents, so neuroimaging often is used for reassurance that the primary headache diagnosis is correct. The authors of two recently published articles evaluated the role of neuroimaging in children with headache. In a prospective cohort study, Tzse et al evaluated the prevalence of historical "red flags" and their association with intracranial abnormalities in 224 healthy children 2-17 years of age who were evaluated for headaches in the ED. The ED physicians completed standardized forms to document headache characteristics and associated symptoms, along with examination findings. At least one presumed historical "red flag" was found in 87.9% of the children, including headache upon awakening from sleep (34.8%), headache noted with or soon after awakening in the morning (39.7%), and headaches increasing in frequency, duration, and severity (40%, 33.1%, and 46.3%, respectively). Children who were not imaged in the ED received a four-month telephone follow-up.

In the 33% of children who received ED neuroimaging, the prevalence of emergent, serious, and incidental intracranial abnormalities was 1%, 1.5%, and 7%, respectively. Fifty-two of 55 children who underwent ED neuroimaging for a documented reason (as opposed to "no specified reason") were noted to have historical red flags, such as headaches on awakening from sleep (46.1%), headaches with or soon after morning awakening (26.9%), or headaches of increasing frequency (19.2%). The authors concluded that while historical red flags are common in children presenting with headaches to the ED, their presence is associated with a low risk of emergent intracranial abnormalities.

Occipital head pain in children has been considered a red flag to indicate a secondary headache. Irwin's review of the medical literature determined that 0-4.1% of children with occipital headaches and normal neurological examinations demonstrate significant findings on neuroimaging. Migraine was the most likely etiology for occipital headaches, which are noted in up to 20% of children with headaches. Occipital headaches in neurologically normal children are no more likely to be associated with intracranial pathology than headaches localized to other cranial locations.

■ COMMENTARY

The question "Is brain imaging needed to diagnose a headache?" plagues patients, parents, physicians, and payers. Clearly, an associated abnormality on neurological examination dictates brain imaging. The more common and more complicated scenario involves a seemingly characteristic history of a primary headache disorder, a normal neurological examination, and a patient skeptical of the proffered diagnosis. Wang et

al used a "belt-and-suspenders" approach to diagnose primary headache disorders and then image both headache patients and headache-free controls, finding no difference in significant brain lesions. The value of clinical and computer diagnostic skills is reassuring, but the authors emphasized the importance of time and expertise in obtaining a detailed neurological history and in performing an appropriate neurological exam prior to deciding that imaging is not indicated. Historically, imaging advocated with some types of primary headaches, such as side-locked headaches including trigeminal autonomic cephalgias and cluster headaches.

This study and personal experience indicate that even with these side-locked headaches, imaging adds little to diagnostic accuracy if the history is characteristic and the examination is normal. Some pediatric red flags, such as morning and occipital headaches, appear to be of little significance and should no longer elicit a knee-jerk response to image. A detailed history, an appropriate examination, and a thoughtful approach should lead to a focused approach to ordering brain imaging studies in patients with headaches. However, if brain imaging is deemed appropriate, then an MRI scan, as opposed to a CT scan, generally should be obtained. ■

ABSTRACT & COMMENTARY

LDL Cholesterol: How Low Do We Go?

By Michael H. Crawford, MD

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

SYNOPSIS: A meta-analysis of 29 cholesterol-lowering outcome studies with baseline average low-density lipoprotein (LDL) cholesterol levels ≤ 70 mg/dL showed consistent major adverse cardiovascular event risk reductions down to average LDL levels of 21 mg/dL without any increase in adverse events.

SOURCES: Sabatine MS, Wiviott SD, Im K, et al. Efficacy and safety of further lowering of low-density lipoprotein cholesterol in patients starting with very low levels: A meta-analysis. *JAMA Cardiol* 2018:3:823-828.

Gotto AM Jr. Low-density lipoprotein cholesterol and cardiovascular risk reduction. How low is low enough without causing harm? *JAMA Cardiol* 2018:3:802-803.

With the advent of PCSK9 inhibitors, low-density lipoprotein cholesterol (LDL-C) now can be reduced to very low levels. The current guidelines recommend high-intensity statins regardless of the LDL-C level in patients with vascular disease or at high risk for developing it.

Investigators sought to evaluate the efficacy and safety of further lowering LDL-C in patients with average levels of ≤ 70 mg/dL at baseline by performing a meta-analysis of 29 randomized, double-blind, controlled trials of aggressive LDL-C-lowering therapy when the average baseline LDL-C was ≤ 70 mg/dL. The primary outcome was a combination of coronary death, myocardial infarction, ischemic stroke, or coronary revascularization over five years. Safety outcomes included myalgias/myositis, elevated liver enzymes, new onset diabetes, hemorrhagic stroke, and cancer. Three trials concerned non-statin drugs (ezetimibe, evolocumab, anacetrapib) added to statins. The other 26 were statin trials.

The statin trials reduced LDL-C from 66 mg/dL to levels not reported. The three non-statin plus a statin trials lowered LDL-C from a baseline of 63-70 mg/dL to 11-45 mg/dL. The overall relative risk of the primary endpoint was 0.79 (95% confidence interval, 0.71-0.87; $P < 0.001$). None of the safety endpoints were altered significantly by LDL-C lowering to median levels of 21 mg/dL.

The authors concluded that there was a consistent reduction in major adverse cardiovascular (CV) events in high CV risk patients with median LDL-C levels of 63 mg/dL, with further LDL-C reduction to a median of 21 mg/dL, without any observed adverse effects.

■ COMMENTARY

The latest cholesterol management guidelines (2013) abandoned LDL-C target levels in favor of using risk of CV events as the determinant of therapy. This was understandable given the lack of data or consensus on LDL-C targets. Also, it was well known that LDL-C levels alone do not predict risk of CV events accurately for primary prevention. Also, it was known that secondary prevention was driven by the mantra that whatever the LDL-C reading, it was too high. However, age heavily influenced the risk calculator to the point that most men > 65 years of age would qualify for statin therapy. Thus, many cardiologists have used

a hybrid system that still considers LDL-C levels, favoring treatment for higher levels. Even the guidelines abandoned the risk equation if LDL-C was > 190 mg/dL.

This meta-analysis demonstrates that there is a 22% reduction in CV events for every 39 mg/dL reduction in LDL-C, down to LDL-C levels of about 20 mg/dL, regardless of baseline LDL-C. However, the higher the LDL-C, the greater the benefit. Also, this study showed that the benefit was independent of the drug used at the same LDL-C level. In addition, the results were remarkably consistent across the 29 trials included, which strengthens the validity of this meta-analysis. Finally, the reduction in CV events was accomplished without an increase over placebo in adverse effects. On the other hand, the non-statin trials were of a relatively short duration. Some adverse events with statins were not observed for more than 20 years. Thus, long-term surveillance of newer drugs still is necessary.

Unfortunately, this study did not establish new targets for LDL-C. However, the authors demonstrated at least short-term safety to a median LDL-C level of about 20 mg/dL. But there were few subjects with very low levels in the meta-analysis. Data from newborns reveal LDL-C levels of 22-45 mg/dL. Perhaps this should be our target range, especially for secondary prevention. Accordingly, some have recommended < 50 mg/dL but > 20 mg/dL for secondary prevention, which this study would support. What the levels should be for primary prevention is not considered.

Current belief is < 100 mg/dL or < 70 mg/dL, but the results of this study suggest lower may be better. We await more studies and the expected revision of the 2013 guidelines to answer these questions. ■

ABSTRACT & COMMENTARY

Does CPAP Improve the Sex Lives of People With Obstructive Sleep Apnea?

By Alan Z. Segal, MD

Associate Professor of Clinical Neurology, Weill Cornell Medical College

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

SOURCE: Jara SM, Hopp ML, Weaver EM. Association of continuous positive airway pressure treatment with sexual quality of life in patients with sleep apnea: Follow-up study of a randomized clinical trial. *JAMA Otolaryngol Head Neck Surg* 2018;144:587-593.

When faced with the possibility of continuous positive airway treatment (CPAP) therapy for obstructive sleep apnea (OSA), patients commonly balk, especially if they fear that this potentially unromantic therapy will affect their sex life adversely. This report from Jara et al suggests otherwise. Data were derived from a 25-point Snore Outcome Scale (SOS), which included two sex-related options: "Because of medical problem, unable to have sexual relations" and "Lack of desire for sexual relations." This was scored on a 0-5 scale (5 was the worst). Specifics regarding sexual function were limited, as data were derived from only these two points on a general scale (the SOS-25) rather than a predetermined sex-specific questionnaire. The cohort included 182 participants (63% men) with severe OSA. There was a significant improvement in SOS score of -0.7 among CPAP users compared with -0.1 among nonusers. This effect persisted in a multivariate analysis. However, in a specific subgroup analysis using only gender, the benefit was restricted to women. There was a 1.3-point improvement in women (95% confidence interval [CI], 0.5-2.18), but only a 0.16-point difference in men (95% CI, -0.26 to 0.58). The authors did not provide any theories to explain this sex difference.

■ COMMENTARY

Among men using CPAP, prior noncontrolled case series have suggested an improvement in sexual function, albeit primarily among subjects who reported prior sexual difficulties. Although hormonal effects have been implicated in OSA, no one has confirmed that low testosterone is a consequence of sleep-disordered breathing or that testosterone can rise with the use of CPAP. However, factors that clearly can improve with CPAP, such as weight gain and poor sleep quality, have shown a definite relationship to testosterone levels.

Among women, other researchers have contradicted this study, failing to show improvements in sexual function or distress with CPAP use. Taking a more granular approach than merely two questions from the SOS-25, other studies used detailed female-specific scales of sexual function, distress, and overall satisfaction. ■

PHARMACOLOGY UPDATE

Baloxavir Marboxil Tablets (Xofluza)

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

Dr. Elliott is Assistant Clinical Professor of Medicine, University of California, San Francisco.
Dr. Chan is Associate Clinical Professor, School of Pharmacy, University of California, San Francisco.

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

For the first time in nearly 20 years, the FDA has approved a new antiviral drug for the treatment of influenza. Baloxavir marboxil is a prodrug for baloxavir, which is the first in the class of polymerase acidic endonuclease inhibitors. It differs from oseltamivir, which is an influenza neuraminidase inhibitor. Baloxavir received a priority review and is distributed as Xofluza.

INDICATIONS

Baloxavir is indicated for the treatment of acute uncomplicated influenza in patients ≥ 12 years of age who have shown symptoms for no more than 48 hours.[1] Prescribers should consider currently available surveillance information on influenza virus drug susceptibility patterns and treatment effects before prescribing baloxavir.[1]

DOSAGE

The dose is a single tablet taken orally within 48 hours of symptom onset.[1] The dose is 40 mg for patients who weigh between 40 kg and 80 kg. For those patients ≥ 80 kg, the dose is 80 mg. The tablets may be taken without regard to meals. Coadministration with food or drugs containing polyvalent cations (e.g., dairy products, calcium-fortified beverages, antacids) should be avoided.

POTENTIAL ADVANTAGES

Baloxavir results in more rapid decline in infectious viral load than oseltamivir and shorter median duration of infectious virus detection (24 hours vs. 72 hours).[2] Because of its long elimination half-life (average, 79 hours), baloxavir can be given as a single dose compared to a twice-daily dose for five days for oseltamivir. Cross-resistance is not expected because of the different target sites for polymerase acidic endonuclease inhibitors and neuraminidase inhibitors.[1]

POTENTIAL DISADVANTAGES

The effectiveness of baloxavir was established mainly in Asian subjects (83%), as the drug was developed in Japan.[1,2] Based on population pharmacokinetics, baloxavir exposure was approximately 35% lower in non-Asians, although this is not considered to be clinically significant.[1] Effectiveness in patients at high risk of influenza complications (age > 65 years, comorbidities) has not been reported. Based on limited data, baloxavir may be less effective against influenza B.[1] Polyvalent-containing foods and drugs significantly decrease the absorption of baloxavir.[1]

COMMENTS

The efficacy and safety of baloxavir was evaluated in two randomized, double-blind studies during two different influenza seasons in otherwise healthy subjects with uncomplicated influenza.[1,2] In trial 1 (n = 400 Asians), subjects were randomized to a single-dose of baloxavir (10 mg, 20 mg, or 40 mg) or placebo. In trial 2 (n = 1,436; 78% Asians), subjects were randomized to baloxavir 40 mg (body weight < 80 kg) or 80 kg (body weight ≥ 80 kg), oseltamivir (75 mg twice daily × five days), or matching placebo. The primary endpoint was time to alleviation of symptoms (start of regimen until all seven symptoms were rated as absent or mild for at least 21.5 hours). The seven symptoms included cough, sore throat, headache, nasal congestion, feverishness or chills, muscle or joint pain, and fatigue. These were assessed on a four-point scale. Virologic endpoints included infectious virus and viral RNA titers.[2] Virus type mainly was influenza A/H1N1 (63% in trial 1) and A/H3N2 (90% in trial 2).

Overall median times to alleviation of symptoms were 50 hours for baloxavir (40 mg) vs. 78 hours for placebo in trial 1 and 54 hours vs. 80 hours, respectively, in trial 2. Benefit was evident by day 2. There was greater benefit if treatment was initiated within 24 hours of onset of symptoms.[2] The median time to fever resolution was shorter with baloxavir compared to placebo (24.5 hours vs. 42 hours). Baloxavir was associated with a more rapid decline in infectious viral load compared to placebo or oseltamivir.[2] However, the median times to alleviation of symptoms were similar between baloxavir and oseltamivir (53.5 hours vs. 53.8 hours). The median time to return to usual health was shorter with baloxavir compared to oseltamivir but did not reach statistical significance (129 hours vs. 160 hours; $P = 0.06$).

Approximately 10% of those treated with baloxavir developed viral mutation, mainly with viral type A(H3N2), leading to resistant variants.[2] Adverse events deemed related to treatment regimens were more common with oseltamivir (8.4% vs. 4.4%).[2] There was no difference in the frequency of

complications that resulted in antibiotic use (3.5% with baloxavir, 4.3% with placebo, and 2.4% with oseltamivir).[2]

CLINICAL IMPLICATIONS

Baloxavir provides a single-dose treatment that is at least as effective as oseltamivir for five days. The CDC recommends prompt use (within 48 hours of illness onset) of antivirals, particularly in patients at high risk of developing flu-related complications.[3,4] The authors of a recently completed clinical trial compared baloxavir, placebo, and oseltamivir in subjects at high risk of influenza complications, but the results have not been reported yet.[5] The drug's wholesale acquisition cost has been set at $150 compared to $87 for a five-day course for generic oseltamivir. ■

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5. ClinicalTrials.gov. Study of S-033188 (baloxavir marboxil) Compared with placebo or oseltamivir in patients with influenza at high risk of influenza complications (CAPSTONE 2). Available online at: https://bit.ly/2QIDalx. Accessed Nov. 5, 2018.

CME QUESTIONS

1. **International visitors to the United States are at risk of becoming ill with which of the following?**
   a. Influenza
   b. Dengue fever
   c. Lyme disease
   d. All of the above

2. **In which state would a resident or visitor be most likely to acquire infection with *Angiostrongylus cantonensis*?**
   a. Florida
   b. Hawaii
   c. New Mexico
   d. Rhode Island

3. **Which historical red flag is most likely to correlate with a significant neuroimaging abnormality?**
   a. Occipital head pain in a child
   b. Headache present on awakening
   c. Headache noted in the morning after awakening
   d. Headache associated with transient monocular vision loss

4. **In a recent meta-analysis of 29 trials in which baseline low-density lipoprotein cholesterol (LDL-C) was ≤ 70 mg/dL, the lowest average LDL-C level that was safe and efficacious was:**
   a. 5 mg/dL.
   b. 12 mg/dL.
   c. 21 mg/dL.
   d. 50 mg/dL.

5. **Obstructive sleep apnea may result in sexual dysfunction.**
   a. True
   b. False

CME OBJECTIVES

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

- describe new findings in the differential diagnosis and treatment of various diseases;
- describe the advantages, disadvantages, and controversies surrounding the latest advances in the diagnosis and treatment of disease;
- identify cost-effective treatment regimens;
- explain the advantages and disadvantages of new disease screening procedures.