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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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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 dem-

onstrated 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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2. Vocale C, et al. Toscana virus infections in northern Italy: Laboratory and clinical evaluation. *Vector-borne and Zoonotic Diseases* 2012;12:526-9.

CDC Expands HCV Testing, Refers HCW Issue to SHEA

Targeting undiagnosed infections

Conceding that the effectiveness of risk-based hepatitis C virus testing has plateaued, public health officials are rolling the dashboard dice to capture the grand-

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daddy of all birth cohorts: Baby Boomers.

The Centers for Disease Control and Prevention recommends that millions of Americans born from 1945 through 1965 get a one-time test for HCV.

Though many people may be completely unaware they are infected for years — they don't call it the "silent epidemic" for nothing — by the time they become symptomatic they may need to get in line for a liver transplant. Some 15,000 Americans, most of them baby boomers, die each year from HCV-related illness, such as cirrhosis and liver cancer. Deaths have been increasing steadily for more than a decade and are projected to grow significantly in coming years. The CDC estimates that HCV testing of baby boomers could identify more than 800,000 additional people with the virus.

With newly available therapies that can cure up to 75% of infections, expanded testing — along with linkage to appropriate care and treatment — could save a lot of livers and more than 120,000 actual lives, the CDC estimates. Indeed, with the development of protease inhibitors that can lower HCV viral counts as well as new antiviral drugs, there are more treatment options to offer the HCV infected.

The CDC's previous HCV recommendations called for testing only individuals with certain risk factors (i.e. blood transfusion prior to screening improvements in 1992, IV drug use). According to the CDC, baby boomers are five times more likely than other adults to be infected with HCV. Or put another way, more than 75% of the adults with HCV are in the famous birth cohort. In any case, there should be a lot more of them out there with HCV than presently detected, in part, because HCV is such a transmissible virus.

"Hepatitis C is actually a very infective virus — at least 10 times more so than HIV," says **Bryce Smith**, PhD, lead health scientist in the CDC Division of Viral Hepatitis. "HCV can live outside the body for as long as seven days, as we have seen with some of these outbreaks. One of the reasons that we recommend that anyone who has been on chronic hemodialysis be tested for HCV is just because there is a reasonable likelihood that they have been exposed to someone else's blood."

Somewhat surprisingly, the virus is not efficiently transmitted via sexual contact.

"The data is equivocal on sexual transmission, but we do know that sexual transmission does sometimes happen," he says. "The data kind of go back and forth on this particular point and right now we don't have a specific recommendation related to using condoms or using barrier methods. For example, we don't recommend that for long-term couples or 'sero-discordant' couples, where there is one person with [HCV] and one person without."

Is the CDC recommending that hospitals and health care providers routinely offer HCV tests to all their patients that fall within this age range?

"Yes," Smith says, though adding the caveat "local laws tend to [dictate] exactly how things like that can happen in terms of getting consent from the patient or whether it can be considered part of their routine blood work. Local laws will guide that, but it is definitely our recommendation that anyone born within 1945 through 1965 should be tested for HCV. Just one time."

Well, possibly two. A patient whose initial HCV antibody test is reactive is considered to either have current HCV infection or have had an HCV infection in the past that has subsequently resolved. To identify people with active HCV infection, those who test anti-HCV positive should be subsequently tested with a nucleic acid test (NAT).

"In essence it is kind of a two staged series," Smith says. "The first test is an antibody test. It tells you whether or not there is [HCV] antibody in the bloodstream, and again it is a very common and relatively inexpensive test. That will tell whether or not the patient has ever been infected with hepatitis C. We estimate that about 75% of people who have ever been infected go on to be chronically infected. [If they are positive], a second test has to be done to look for the presence of the virus itself in the bloodstream."

If so, the patient needs to get a full medical evaluation that would include an identification of the specific HCV genotype, measurement of their viral load and the best options for treatment. The NAT test could be done in a hospital, or the patient could be referred to their primary care physician or other "medical home" for the follow-up testing, he says.

As always, the question arises of who will pay for the testing. "Everyone has different types of insurance, but by and large it is our understanding that this [antibody] test is considered to be pretty routine," Smith says. "It is available just about everywhere. It is a test that generally speaking is covered by most insurance [programs]. We don't expect that to be a significant problem. We have looked really closely at the costs of this strategy and found that it is actually quite cost effective. It really is very similar to other routine preventive services like colorectal and cervical cancer screening or breast cancer screening.

Asked if health care workers within the targeted age range are also recommended for HCV testing, Smith says, "We are not making any distinction. I would say anyone who was born from 1945 to 1965 — who is a baby boomer — should be tested for hepatitis C. That is really regardless of their profession."

Of course the identification of HCV-positive health care workers raises the thorny issues of provider-to patient transmission, work restrictions and informing patients — much as it did when the CDC finally went to a universal HIV test recommendation in 2006. The CDC referred inquiries on the issue to the 2010 guidelines by the Society for Healthcare Epidemiology of America (SHEA).[1] Those guidelines are quite specific in recommending recurrent testing for HCV viral counts and

applying work restrictions to workers who perform so called exposure-prone invasive procedures. The precautions to be taken range from double-gloving to an outright restriction on performing certain procedures if the worker has a high viral load — defined as equal to or greater than 10^4 genome equivalents per milliliter of blood for HCV.

However, in what some say was an undermining omission, the guideline did not address routine testing of surgeons and other OR personnel — except to say that testing should not be mandatory and that health care workers performing invasive, exposure-prone procedures are "ethically obligated" to know their status. The European Consortium could not reach consensus on HCV-infected providers. The United Kingdom guideline states that HCV-infected providers with circulating RNA should not conduct exposure-prone procedures.

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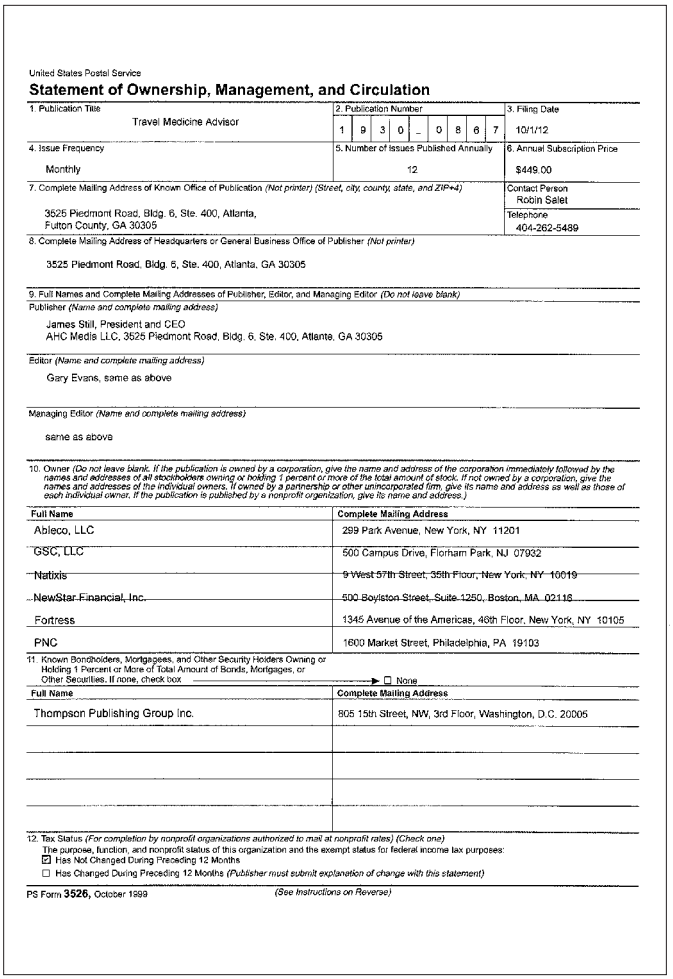

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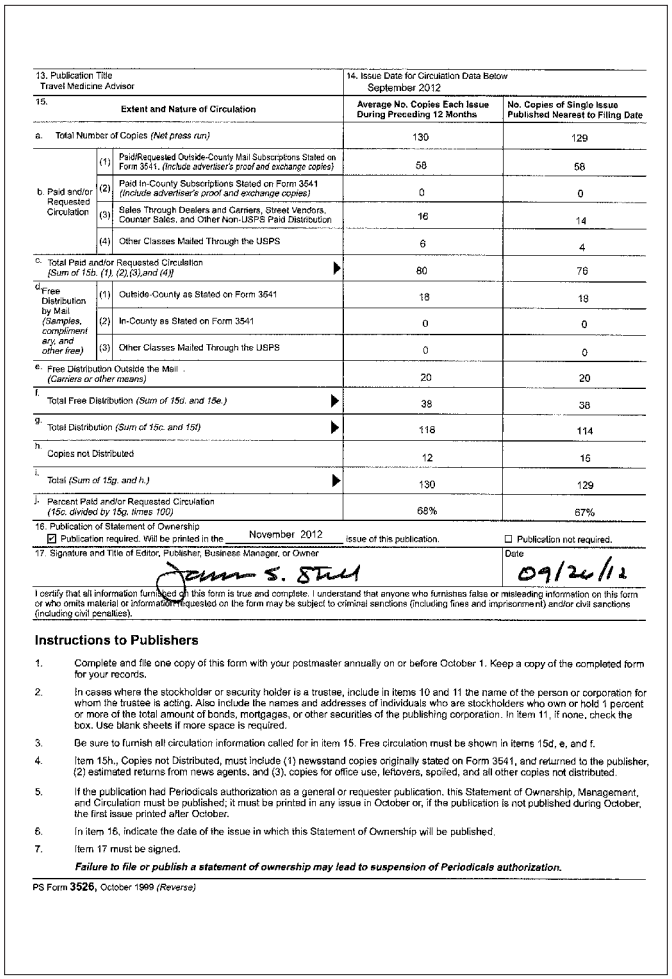

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PHARMACOLOGY WATCH

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Do Benzodiazepines Cause Dementia in the Elderly?

In this issue: Dementia and benzodiazepines; effectiveness of omega-3 fatty acid and *Ginkgo biloba* supplements; and FDA actions.

Benzodiazepines and dementia

Can benzodiazepines increase the risk for dementia? Researchers in France studied 1063 men and women with an average age of 78 who were free of dementia and did not start taking benzodiazepines until they had been followed for at least 3 years. During a 15-year follow-up, 253 cases of dementia were confirmed. New use of benzodiazepines occurred in 9% of the study population and was associated with an increased risk of dementia (32% benzodiazepine group vs 23%, adjusted hazard ratio 1.60, 95% confidence interval [CI] 1.08-2.38). After correcting for the existence of depressive symptoms as well as age and diabetes, the hazard ratio was unchanged. A secondary analysis looking at participants who started benzodiazepines at different times during follow-up also showed an elevated risk of dementia. Results of the complementary, nested, case-control study showed that ever use of benzodiazepines was associated with an approximate 50% increased risk of dementia compared with never users. The authors conclude that in this prospective, population-based study new use of benzodiazepines was associated with a significantly increased risk of dementia. They further conclude that "indiscriminate widespread use should be cautioned against" (*BMJ* 2012;345:e6231). The obvious criticism of the study was the presence of confounders — whether use of benzodiazepines was a marker for early onset dementia rather than a cause. While the authors feel the study was carefully controlled, selection bias cannot be completely ruled out. They further state that the research should be done on younger patients to see if starting benzodiazepines at ages younger than 65 may have deleterious effects. They also recommend that "physicians and regulatory agencies should consider the increasing evidence of potential adverse effects of this drug class for the general population." ■

Popular supplements' use questioned

Two popular supplements — omega-3 fatty acids and *Ginkgo biloba* — may be of limited value, according to two recent studies. Omega-3 fatty acids are thought to have a number of benefits, including lowering triglyceride levels, preventing arrhythmias, decreasing platelet aggregation, and lowering blood pressure. But the fish oil supplement's ability to prevent major cardiovascular events has been debated in the literature. Twenty studies of nearly 67,000 patients were included in a meta-analysis looking at the effect of omega-3 on all-cause mortality, cardiac death, sudden death, myocardial infarction, and stroke. After correcting for dose and comorbidities, there was no difference in the absolute or relative risk of any of the outcomes associated with omega-3 supplementation. The authors concluded that marine-derived omega-3 polyunsaturated fatty

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acid supplementation was not associated with a lower risk of all-cause mortality, cardiac death, sudden death, myocardial infarction, or stroke (*JAMA* 2012;308:1024-1033).

Ginkgo biloba for the prevention of Alzheimer's disease (AD) was studied in a randomized, parallel group, double-blind, placebo-controlled trial of adults age 70 years or older who spontaneously reported memory complaints to their primary care physician in France. Patients were randomized to a twice per day 120 mg standardized *Ginkgo biloba* extract or matching placebo and followed for 5 years. The primary outcome was conversion to probable AD. More than 2800 patients were enrolled with about 1400 patients in each group. By 5 years, 61 participants in the ginkgo group were diagnosed with AD vs 73 in the placebo group (hazard ratio 0.84, 95% CI 0.60-1.18; $P = 0.306$). Adverse events were the same between both groups and mortality was roughly the same as well. Sixty-five participants in the ginkgo group had a stroke compared to 60 in the placebo group ($P = 0.57$). The authors conclude that long-term use of standardized *Ginkgo biloba* extract did not reduce the risk of progression to AD compared to placebo (*Lancet Neurology* 2012;11:851-859). ■

FDA actions

The FDA has approved teriflunomide for the treatment of relapsing forms of multiple sclerosis (MS). The approval was based on a 2-year study in which the drug reduced relapses by nearly a third compared to placebo — results that are about the same as other MS drugs and no better than Merck's popular injectable interferon beta 1a (Rebif). Side effects include diarrhea, abnormal liver function tests, nausea, and hair loss. It should not be used during pregnancy. Teriflunomide has the advantage of being a once-daily oral medication, the second oral MS medication after Novartis' fingolimod (Gilenya). Teriflunomide will be marketed by Sanofi Aventis as Aubagio. A third oral MS medication, Biogen Idec's BG-12, was recently found to reduce MS relapses by about 50% (*N Engl J Med* 2012;367:1087-1097; 1098-1107). BG-12 is not yet approved by the FDA, but a decision is expected before the end of the year.

The FDA has delayed the approval of apixaban (Eliquis) once again. Pfizer and Bristol-Myers Squibb's novel oral anticoagulant (NOAC) was expected to be approved last spring after publication of the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trial, which showed that the drug was effective in preventing strokes in patients with non-valvular atrial fibrillation — data that suggested that the drug was perhaps even more effective than the two other NOACs, dabigatran (Pradaxa) and rivaroxaban (Xarelto). In June, the FDA told the manufacturers they needed "additional information on data management and verification from the ARISTOTLE trial." Now, the agency says that the review date will be March 17, 2013. No reason was given by the FDA for the delay.

About 25% of Internet consumers have purchased prescription medications online, while at the same time, the prevalence of fraudulent Internet pharmacies has grown. The FDA has now launched a national campaign to raise public awareness called BeSafeRx – Know Your Online Pharmacy, a resource that provides patients and caregivers with a better understanding of who they are buying from, and makes sure the medication they buy matches what their doctor prescribed. The FDA recommends that patients only buy medications from online pharmacies that require a prescription, are located in the United States, have a licensed pharmacist available for consultation, and are licensed by the patient's state board of pharmacy. More information can be found at www.FDA.gov/BeSafeRx.

The FDA has approved enzalutamide to treat men with late-stage, castration-resistant prostate cancer under the agency's priority review program. The drug was approved based on a study of nearly 2000 men with metastatic prostate cancer who had been previously treated with docetaxel. Men treated with enzalutamide lived an average of 18.4 months vs 13.6 months for men treated with placebo. Enzalutamide is co-marketed by Astellas and Medivation as Xtandi.

The FDA has also approved a new agent for the treatment of advanced colorectal cancer. Regorafenib is a multi-kinase inhibitor that was also approved under the FDA's priority review program. In a study of 760 patients with previously treated metastatic colorectal cancer, regorafenib extended survival about 45 days to 6.4 months from 5 months for placebo as well as progression-free survival of 2 months vs 1.7 months for placebo. Regorafenib is marketed by Bayer as Stivarga. ■