Richard Lappin, MD, PhD, Associate Editor, First EDition

WHO Declares 'Public Health Emergency' for Microcephaly Linked to Zika Virus

BY MARY ELLEN SCHNEIDER
FRONTLINE MEDICAL NEWS

The World Health Organization (WHO) has declared a "public health emergency of international concern" related to the clusters of microcephaly and other neurological complications reported in Brazil and earlier in French Polynesia. Though there is a strong association between these cases and the Zika virus, a causal link still has not been scientifically proven, according to the WHO.

The WHO's emergency declaration clears the way for the international health community to move forward with a coordinated response. Dr Margaret Chan, WHO Director-General, said her organization plans to take a number of precautionary measures, including improving surveillance and detection of infections, congenital malformations, and neurological complications. They will also work with countries to intensify control of mosquito populations and help expedite the development of diagnostic tests and vaccines to protect at-risk populations.

The recommendations came after a February 1 meeting of the International Health Regulations Emergency Committee, which Dr Chan convened in response to the Zika virus outbreak and the observed increase in neurological disorders and neonatal malformations.

The group of 18 experts advised that the clusters of microcephaly and other complications constitute an "extraordinary event and a public health threat to other parts of the world." The group did not recommend any restrictions on travel or trade with areas where the Zika virus transmission is ongoing, however.

"At present, the most important protective measures are the control of mosquito populations and the prevention of mosquito bites in at-risk individuals, especially pregnant women," Dr Chan said during a press briefing.

Dr Chan said it's unclear how long it will take to determine if Zika virus is causing the uptick in microcephaly and other congenital malformations and neurological abnormalities, but health officials are working to set up case-control studies.

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Preparing for Zika Virus Outbreaks

BY DEEPAK CHITNIS
FRONTLINE MEDICAL NEWS

The recent spike in Zika virus cases in Central and South America brings with it the alarming risk—and even the expectation—of outbreaks occuring in the United States. How should US-based clinicians prepare for the inevitable?

"The current outbreaks of Zika virus are the first of their kind in the Americas, so there isn't a previous history of Zika virus spreading into the [United States]," explained Dr Joy St. John, director of surveillance, disease prevention, and control at the Caribbean Public Health Agency in Trinidad.

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But now that the virus has hit the United States, with a confirmed case in Texas and more emerging since then, Dr St. John said the most important thing is for US health care providers to recognize the signs and symptoms of Zika virus infection. Carried and transmitted by the *Aedes aegypti* species of mosquito, Zika virus symptoms are relatively mild, consisting predominantly of maculopapular rash, fever, arthralgia, myalgia, and conjunctivitis. Only one in five individuals with a Zika virus infection develop symptoms, but patients who present as such and

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who have traveled to Central or South America in the week prior to the onset of symptoms should be considered likely infected.

"At present, there is no rapid test available for diagnosis of Zika," said Dr St. John. "Diagnosis is primarily based on detection of viral RNA from clinical serum specimens in acutely ill patients."

To that end, polymerase chain reaction (PCR) testing can be conducted on serum samples collected within 3 to 5 days of symptom onset. Beyond that, elevated levels of immunoglobulin M antibodies can be confirmed by serology, based on the neutralization, seroconversion or four-fold increase of Zika-specific antibodies in paired samples. However, Dr St. John warned that "Due to the possibility of cross reactivity with other viruses, for example, dengue, it is strongly recommended samples be collected early enough for PCR testing."

Zika and Pregnancy

Zika virus has now been identified in 14 countries and territories worldwide, and while most infected patients experience relatively mild symptoms, Zika becomes very concerning when it infects a pregnant woman, as there have been cases of microcephaly in children whose mothers were infected with Zika virus during pregnancy. Although the association of microcephaly with Zika virus infection during pregnancy has not been definitively confirmed, the Centers for Disease Control and Prevention (CDC) have already issued a warning to Americans—particularly pregnant women—about traveling to high-risk areas.

"Scientifically, we're not 100% sure if Zika virus is causing microcephaly, [but] what we're seeing is in certain Brazilian districts, there's been a 20-fold increase in rates of microcephaly at the same time that there's been a lot more Zika virus in pregnant women," explained Dr Sanjaya Senanayake of Australian National University in Canberra.

According to data from the CDC, 1,248 suspected cases of microcephaly had been reported in Brazil as of November 28, 2015, compared to the annual rate of just 150 to 200 such cases during 2010 through 2014. "Examination of the fetus [and] amniotic fluid, in some cases, has shown Zika virus, so there seems to be an association," Dr Senanayake clarified, adding that "the [ANVISA – Brazilian Health Surveillance Agency] has told women in certain districts where there's been a lot of microcephaly not to get pregnant."

Brazil is set to host millions of guests from around the world as the 2016 Olympics get underway in only a few months' time. Women who are pregnant or anticipate becoming pregnant should consider the risks if they are planning to travel to Rio de Janeiro. The risk of microcephaly does not apply to infected women who are not pregnant, however, as the CDC states that "Zika virus usually remains in the blood of an infected person for only a few days to a week," and therefore "does not pose a risk of birth defects for future pregnancies."

Dr St. Joy also stated that "public health personnel are still cautioning pregnant women to take special care to avoid mosquito bites during their pregnancies," adding that the "[Pan-American Health Organization] is working on its guidelines for surveillance of congenital abnormalities."

Clinical Insights

With treatment options so sparse—there is no vaccine or drug available specifically meant to combat a Zika virus infection—what can healthcare providers do for their patients? The CDC advises health care providers to "treat the symptoms," which means telling patients to stay in bed, stay hydrated, and, most importantly, stay away from aspirins and NSAIDs "until dengue can be ruled out to reduce the risk of hemorrhage." Acetaminophen or paracetamol are safe to use, in order to mitigate fever symptoms.

Those who are infected are also advised to stay indoors and remain as isolated as possible for at least a week after symptoms first present. While the risk of a domestic outbreak is probably low, Dr St. John said, the more exposure a Zika virus-infected individual has to the outside world, the more likely they are to be bitten by another mosquito, which can then carry and transmit the virus to another person.

"Chikungunya and dengue virus, which are transmitted by the same vectors [as Zika virus], have not managed to establish ongoing transmission in the United States despite repeated importations, [so] it is likely that Zika virus' spread would follow a similar pattern," Dr St. John noted.

Though rare, sexual transmission of Zika virus has also been found in at least one case, although it had been previously suspected for some time. In December 2013, a 44-year-old Tahitian man sought treatment for hematospermia. Analysis of his sperm, however, found Zika virus, indicating possible sexual transmission of the virus.

"The observation that [Zika virus] RNA was detectable in urine after viremia clearance in blood suggests that, as found for [dengue] and [West Nile virus] infec-

tions, urine samples can yield evidence of [Zika virus] for late diagnosis, but more investigation is needed," the study concluded.

"The best way to control all this is to control the mosquito," said Dr Senanayake. "You get a four-for-one deal; not only do you get rid of Zika virus, but also chikungunya, dengue, and yellow fever." Dr Senanayake added that advanced research is currently underway in mosquito control efforts, including the idea of releasing mosquitoes into the wild that have been genetically modified so they cannot breed.

Now that the Illinois Department of Health has confirmed two new cases of Zika virus infection in that state, with other new cases cropping up in Saint Martin, Guadeloupe, and El Salvador, providers should remain vigilant, taking note of patients who have traveled to afflicted regions and show mosquito bites. Person-to-person transmission is "rare as hen's teeth," said Dr Senanayake, which is to say, it is highly unlikely to occur. Nonetheless, he said information and communication is the best way to ensure that Zika virus does not spread widely in the United States.

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Study Characterizes Intracerebral Hemorrhage With New Oral Anticoagulants

BY MARY ANN MOON

FROM *JAMA NEUROLOGY*

Vitals

Key clinical point: Intracerebral hemorrhage (ICH) related to new oral anticoagulants frequently involves hematoma expansion and does not appear to respond to prothrombin complex concentrate.

Major finding: Mortality was 28%; 65% of survivors had unfavorable outcomes; and substantial hematoma expansion occurred in 38% of patients.

Data source: A prospective, multicenter, observational study involving 61 patients treated during a 3-year period in Germany.

Disclosures: The RASUNOA registry was supported by the University Hospital Heidelberg. Dr Purrucker reported receiving support from Pfizer unrelated to this study, and his associates reported ties to numerous industry sources.

Intracerebral hemorrhage related to non–vitamin-K antagonist oral anticoagulants carries a high mortality and frequently involves hematoma expansion, according to a report published online December 14 in *JAMA Neurology*.[1]

The characteristics and natural history of acute-phase non–vitamin-K antagonist oral anticoagulant (NOAC)-associated intracerebral hemorrhage "are largely unknown," and there are no prospective data concerning hematoma expansion or the effectiveness of prothrombin complex concentrate in limiting that expansion by reversing anticoagulation. Nevertheless, current recommendations suggest that clinicians consider administering prothrombin complex concentrate in this patient population, said Dr Jan C. Purrucker of the department of neurology at Heidelberg (Germany) University and his associates.[1]

Dr Purrucker and his associates performed the ICH substudy of the Registry of Acute Stroke Under New Oral Anticoagulants (RASUNOA), a prospective registry with certified stroke units in Germany. For their substudy, the investigators focused on 61 adults with a mean age of 76 years (range, 46-97 years) who were taking novel anticoagulants (NOACs; [apixaban, dabigatran etexilate, or rivaroxaban]) and had moderate to severe neurologic deficits and a median hematoma volume of 10.8 mL at presentation. Prothrombin complex concentrate was given to 35 (57%).

Mortality was high; 10 (16%) patients died during the acute inpatient stay and 17 (28%) at 3 months. Of the survivors, 65% had an unfavorable outcome. Substantial hematoma expansion—defined as a 33% or greater relative increase or 6 mL or greater absolute increase in intracerebral hemorrhage volume—affected 38% of patients. "This proportion was within the range reported for vitamin-K antagonist–associated intracerebral hemorrhage (36%-56%) and is higher, compared with that related to intracerebral hemorrhage in patients not receiving anticoagulation (12%-26%)," the researchers wrote.

Both larger hematoma volume at baseline (odds ratio

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Views on the News

Hematoma Expansion Was Likely 100%

It is important to note that in the study by Dr Purrucker and his colleagues, the median time from symptom onset to the first brain imaging was 14 hours and that fully 25% of patients presented for treatment more than 22 hours after noticing their initial symptoms. In contrast, patients with spontaneous hypertensive intracerebral hemorrhage present much earlier, usually within 6 hours. This indicates that the bleeding in NOAC-associated hemorrhagic stroke often is gradual and prolonged, an "oozing" process rather than the explosive type of process seen in spontaneous hemorrhagic stroke.

It is almost certain that if this cohort had undergone imaging at 3 hours rather than at 14 hours after symptom onset, the frequency of hematoma expansion would have approached 100% rather than 38%.

Dr Stephan A. Mayer is at Mount Sinai University, New York. He reported having no relevant financial disclosures. Dr Mayer made these remarks in an editorial accompanying Dr Purrucker's report (Mayer, SA. Emergency Reversal of Novel Oral Anticoagulants. Help Is on the Way. JAMA Neurol. *doi:10.1001/jamaneurol.2015.3884).*

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[OR], 2.37) and intraventricular extension at baseline (OR, 8.13) strongly correlated with adverse outcomes. In contrast, prothrombin-complex concentrate failed to limit lesion expansion or avert adverse outcomes. This might be because patients given the treatment tended to have more severe initial neurologic deficits and more unfavorable hematoma location than did those who were not given prothrombin complex concentrate. In any case, "our study design, the limited sample size, and the potential for confounding by indication do not allow any [firm] conclusions regarding a potential association between prothrombin-complex concentrate treatment and outcome," they noted.

1. Parrucker JC, Haas K, Rizos T, et al. Early Clinical and Radiological Course, Management, and Outcome of Intracerebral Hemorrhage Related to New Oral Anticoagulants. *JAMA Neurol.* doi:10.1001/jamaneurol.2015.3682.

FDA Approves Treatment for Chemotherapy, Overdoses, Life-threatening Toxicities

BY ELIZABETH MECHCATIE

FRONTLINE MEDICAL NEWS

Uridine triacetate, a pyrimidine analogue, has been approved for the emergency treatment of fluorouracil or capecitabine overdoses in adults and children, and for patients who develop "certain severe or life-threatening toxicities within 4 days of receiving" these treatments, the Food and Drug Administration (FDA) announced on December 11, 2015.

"Today's approval is a first-of-its-kind therapy that can potentially save lives following overdose or life-threatening toxicity from these chemotherapy agents," Dr Richard Pazdur, director of the office of hematology and oncology products in the FDA's Center for Drug Evaluation and Research, said in the FDA statement.[1] It will be marketed as Vistogard by Wellstat Therapeutics.

Uridine comes in an oral granule formulation that can be mixed into soft foods or, when necessary, administered via a nasogastric or gastrostomy tube, the prescribing information states. The indication is for use after an overdose "regardless of the presence of symptoms," and for treating "early-onset, severe, or life-threatening toxicity affecting the cardiac or central nervous system, and/or early-onset, unusually severe adverse reactions (eg, gastrointestinal toxicity and/or neutropenia) within 96 hours following the end of fluorouracil or capecitabine administration," according to the prescribing information.

Uridine blocks cell damage and cell death caused by fluorouracil chemotherapy, according to the statement.

Uridine was evaluated in two studies of 135 adults and children with cancer treated for a fluorouracil or capecitabine overdose or for early-onset severe or life-threatening toxicities within 96 hours after receiving fluorouracil. Among those treated for an overdose, 97% were alive 30 days after treatment, and among those treated for early-onset severe or life-threatening toxicity, 89% were alive 30 days after treatment. In addition, 33% of the patients resumed chemotherapy within 30 days, according to the FDA statement. Diarrhea, vomiting, and nausea were the most common adverse events associated with treatment.

1. US Food and Drug Administration. FDA approves first emergency treatment for overdose of certain types of chemotherapy [FDA News Release]. December 11, 2015. http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm476919.htm.

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FDA Advisory Committees Support Changing Codeine Contraindications for Children

BY DEEPAK CHITNIS

AT AN FDA ADVISORY COMMITTEE MEETING

SILVER SPRING, MD—Food and Drug Administration advisory committees have voted overwhelmingly to support expanding the current contraindication for codeine to preclude its use for any pain management in all children under age 18 years.

Twenty members of the FDA's Pulmonary-Allergy Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee voted on December 10 for the contraindication. Six members elected to contraindicate for any pain management in children younger than 12 years old, and another two members voted only to contraindicate for children younger than age 6 years. One committee member voted not to make any changes to the current contraindications for codeine.

The joint advisory panel also voted to contraindicate the use of codeine for the treatment of cough in all children younger than age 18 years by a similarly robust margin: 20 members voted for contraindicating in all pediatric patients, five voted to contraindicate only in patients younger than age 12 years, one voted to contraindicate in children younger than age 6 years, and three members voted not to make any changes at all.

The final voting question, asking whether to remove codeine from the FDA monograph for over-the-counter use in treating cough in children, was almost unani-

mously supported by the voting members of both committees. One member supported removing codeine from the monograph only for children under age 2 years.

The decision to vote on approving amendments to the contraindications for codeine use—which would affect not just the monogram, but labeling as well—comes on the heels of the FDA announcing last summer that they would be investigating the safety of codeine-containing drugs in children.

The joint advisory panel cited reports of respiratory depression and death in pediatric patients, variability of codeine metabolism based upon CYP2D6 activity, and the fact that "some regulatory agencies have restricted use of codeine for both cough and analgesia in pediatric patients" as their key reasons for considering the changes to current contraindications, according to Dr Sally Seymour, the FDA's Deputy Director for Safety.

The FDA is not required to follow the advice of its advisory panels. No members of the panel reported any relevant financial conflicts of interest.

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80% of Emergency Physicians Say Mental Health Crisis Response Needs Overhaul

BY WHITNEY MCKNIGHT
FRONTLINE MEDICAL NEWS

Vitals

Key clinical point: A new model of psychiatric ED care is being developed by the Coalition on Psychiatric Emergencies (COPE), to improve care, outcomes, and net costs.

Major finding: 8 in 10 emergency physicians (EPs) believe a lack of training and resources keep them from meeting a growing demand for emergency mental health services.

Data source: American College of Emergency Physicians (ACEP) survey of 1,500 EPs nationwide.

Disclosures: COPE is underwritten in part by Teva Pharmaceuticals.

Emergency medicine professionals have teamed up with mental health workers and patient advocates to call for a new model of care for ED patients in mental health crisis.

The Coalition on Psychiatric Emergencies," is focused on improving the delivery of emergency psychiatric care, and is supported by more than 30 national emergency medicine, mental health, and patient advocate groups, including the ACEP, the American Psychiatric Association, and the National Alliance on Mental Illness (NAMI). The action comes on the heels of a survey that found 80% of 1,500 US EPs think the system for treating people in acute mental health crisis is broken.

"It's time we think about doing things differently," Dr Michael Gerardi, COPE Steering Committee Chair and immediate past president of ACEP, said in a statement. "Through this unique collaboration, the Coalition on Psychiatric Emergencies will focus on developing a more unified treatment model and improving the treatment experience for both patients and health care providers. We want to provide the best care for all our patients and reduce health care costs."

Among its several goals, the coalition seeks to shorten the time between when a person in mental health crisis presents to the ED and is admitted to an inpatient psychiatric bed. In a recent NAMI survey of 1,400 families, 38% waited more than 7 hours in the ED before seeing a mental health professional. For 21% of those families, the wait was more than 10 hours.

The Coalition on Psychiatric Emergencies also seeks adequate education and training for all emergency personnel who care for patients experiencing psychiatric emergencies.

"Emergency department staff need proper training not only on how to handle behavioral health emergencies, but also on how to initiate care for patients who may remain in the ED setting for long periods of time," Dr Lorenzo Norris, director of inpatient psychiatric services at George Washington University Hospital in Washington, DC, said in an interview. "Establishing these new systems will likely require robust funding efforts."

"There is a growing need for change. At our hospital, we have definitely seen an uptick in the number of patients seeking emergency psychiatric care," Dr Norris said. "Our approach has been to hire a clinician whose sole duty is to work collaboratively with patients and ED staff. It's the first step in our ultimate goal of creating an ED behavioral health team that includes a psychiatrist, an emergency physician, nursing staff, social worker, and others who can provide the patient with comprehensive care at the initial point of contact."

Currently in the United States, there are no standard protocols for a psychiatric emergency, according to the National Institute of Mental Health. The online survey was conducted within the ACEP membership between July 1 through 31, 2015. The response rate was 6% and the margin of error of 2.5%.

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