TRAVEL MEDICINE ADVISOR

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AHC Media

Oral Transmission of Chagas Disease: New Epidemiology for an Old Disease

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Drs. Blackburn and Barry report no financial relationships to this field of study.

Synopsis: *Several recent outbreaks of Chagas disease have been due to oral transmission. Although this protozoal infection is classically transmitted by triatomine insects, an emerging recognition of oral transmission could expand our understanding of the distribution for this parasitic infection.*

Source: Shikanai-Yasuda MA, Carvalho NB. Oral transmission of Chagas disease. *Clin Infect Dis.* 2012;54:845-52.

CHAGAS DISEASE IS CAUSED BY THE PROTOZOAN PARASITE *TRYPANOSOMA CRUZI*, endemic only to the Americas. Most cases occur in tropical Central and South America, typically in impoverished communities that impinge upon the rural transmission cycle of this organism. About 8 million people are infected, and transmission classically occurs through the bite of infected triatomines, a subfamily of large bloodsucking insects. Triatomines transmit the parasites through deposition of infected feces following their bites,; parasites are subsequently scratched into the bite wound or a mucous membrane. *T. cruzi* is perpetuated in the wild by a sylvatic transmission cycle between forest-dwelling mammals and triatomines. Human infection usually occurs when settlements impinge upon this sylvatic cycle, leading to disease predominance in rural areas. In addition, human infections occur commonly only in areas with substandard housing, given the preference of these insects to dwell in the nooks and cracks of mud-thatched houses.

In part due to urban migration in many Latin American countries, transmission has been recognized increasingly in urban and peri-urban areas. Although these insects are endemic to the United States, where a few autochthonously transmitted cases have been documented, vector-borne transmission in the U.S. is rare, in part because of high housing standards. Infection can

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also occur through blood transfusion, congenitally from mother to child, and rarely through laboratory accidents or organ transplantation. Overall, the incidence of Chagas disease has been on the decline in recent years due to better vector control and blood screening programs in endemic areas.

Most patients infected with *T. cruzi* remain asymptomatic; a minority develop acute Chagas disease, with symptoms such as fever, lymphadenopathy, hepatosplenomegaly, an erythematous, indurated chagoma at the entry site (or unilateral bipalpebral edema if the innoculation site is the conjunctiva – Romaña's sign), and detectable parasitemia. Acute and severe manifestations rarely occur (e.g., meningoencephalitis, myocarditis), which are fatal in 5-10% of symptomatic patients. Subsequently, most patients enter an asymptomatic indeterminate phase during which they are usually seropositive and sub-patently parasitemic. After years — decades, 10-30% progress to chronic Chagas disease; cardiac Chagas in most of those who develop chronic cardiac disease (e.g., arrhythmias, congestive heart failure, thromboembolism), and gastrointestinal (e.g., megaesophagus, megacolon) or mixed Chagas in others.

The clinical syndrome of orally-acquired Chagas disease is similar to that of vector-borne Chagas, which causes acute symptoms in <5% of infected patients, although the incubation period is longer for orally-acquired disease, and no chagoma nor Romana's sign are seen. The severity of the disease depends in part on the number of parasites ingested and the host's immune response. Treatment of acute Chagas disease is recommended in all recognized cases, preferably with benznidazole, or alternatively nifurtimox.

■ COMMENTARY

Although oral transmission of *T. cruzi* has been described since at least the 1960s, the past decade has seen a dramatic increase in the number of described cases from oral transmission, often in the context of outbreaks. In areas where vector control programs are strong, oral transmission may be a particularly important means of spread to humans. From 2000-2010, over 1,000 acute Chagas disease cases were reported in Brazil, with 71% of these due to oral transmission; most were in areas with good vector control programs.

Although there were just three reported outbreaks of acute Chagas disease from 1968-2000, there have at least been ten since 2001. The largest two outbreaks each involved over 100 people. Overall nearly a dozen deaths occurred in these outbreaks, mostly due to myocarditis / heart failure. The outbreak sources included fruit juices (e.g., acai, guava, orange/ tangerine), sugarcane juice, water, food, and soup. In most cases, crushed triatomines probably contaminated the food/drink, but other sources were possible as well. In many outbreaks, it is likely that unsanitary preparation of food/drink allowed triatomine contamination; in addition, these insects are attracted to light, which may result in high triatomine densities where there is ongoing food preparation. Although sensitive to desiccation, *T. cruzi* appears able to survive in sugar cane juice for 24 hours, based on experimental inoculation studies. *T. cruzi* can also survive in acai juice for many hours,

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including at extremes of pH and temperature.

Although the vectors of *T. cruzi* are largely under control in some countries, eradication of Chagas disease is not feasible because of the zoonotic cycle of *T. cruzi*. In the Amazon, household colonization with triatomines generally does not occur, but the role of acai as a food source and the presence of humans impinging upon the sylvatic transmission cycle have been associated with *T. cruzi* propagation, and may explain why in such a high proportion of acute Chagas cases it appears to be orally-acquired. In other regions of Brazil, the opossum is a source of blood for triatomines, and can contribute to Chagas transmission. Infection can also occur in domestic animals which could perpetuate the transmission cycle in some areas where humans impinge upon *T. cruzi* transmission in forest border zones. Although the Amazon region has seen the most Chagas outbreaks to date, they have occurred both north and south of this region, including in urban areas.[1,2]

Oral transmission of Chagas represents an emerging means of transmission for this disease, and may continue to grow in importance as vector control programs render transmission due to triatomines less important in many areas. A need exists for health education in at-risk areas to diminish the risk of orally acquired Chagas disease.[1] Implementation of measures such as crop cleaning to exclude insects, covering of presses and avoiding operations adjacent to artificial light, pasteurization of commercial acai juice, and keeping vulnerable juice preparations covered are some examples of preventative measures that could help prevent oral transmission of *T. cruzi*.

Several researchers have studied the importance of oral transmission of Chagas disease; however recent outbreaks associated with acai juice have garnered attention to foodborne contamination and transmission. Acute morbidity in orally transmitted infections appears to be more severe than among patients with vector-borne infections.[3] In theory, undercooked meat from infected host reservoir animals could also pose risk for transmission, but laboratory data suggest the infectivity is lower than that for trypomastigotes in crushed triatomines or their feces.[4] ■

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Nodding Syndrome in South Sudan

ABSTRACT AND COMMENTARY

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Neither Dr. Mrelashvili nor Dr. Fischer reports financial relationships to this field of study.

Synopsis: *"Nodding syndrome" is a puzzling and poorly characterized neurologic condition of children characterized by progressive eating-related seizures with nodding of the head and encephalopathy. It mostly occurs in South Sudan, Uganda, and Tanzania.*

Source: Centers for Disease Control and Prevention. "Nodding Syndrome — South Sudan, 2011." *MMWR* 2012; 61:52-54.

In May 2011, an emergency-response team from the US Centers for Disease Control and Prevention (CDC) traveled to South Sudan, attempting to assist in the investigation of the recent geographic clustering of an illness, suspected to be the nodding syndrome. A descriptive study was conducted in two different communities (Maridi and Witto), enrolling a total of 38 matched case-control pairs. While assessing various risk factors, researchers also tried to identify any possible link between the condition and infection with a nematode worm, *Onchocerca volvulus*.

Although current infection with the *O. volvulus* was more prevalent among case-patients in Maridi (88% among case-patients and 44% among controls, $P < 0.001$), no such difference was found in Witto (54% among case-patients and 54% among controls).

Nodding syndrome was not found to be associated with other risk factors, including exposure to munitions, parents' occupations, and various demographic characteristics. Additional analyses of case-series data and additional investigations of exposures related to nutrition are under way. Results of laboratory testing (for vitamins A, B_6, and B_{12}; Onchocerca antibodies; heavy metals; and genetic markers) are pending.

■ COMMENTARY

Nodding syndrome or disease was recognized as a specific entity around the turn of the millennium in what

is now South Sudan.[1] Retrospectively, however, a similar sort of seizure disorder was reported in southern Tanzania in the 1960s.[2,3] Affected children are also often identified in northern Uganda. The condition typically begins between the ages of 5 and 15 years, and the disease is slowly progressive, impairing physical growth and cognitive development and eventually leading to death.[4]

The hallmark of the condition, head nodding, is often brought on by eating [especially beans and starch[1]] or sometimes by cold exposure and occurs as a sudden loss of neck muscle tone and, possibly, upper extremity tone. Many patients go on to develop generalized seizures that are incompletely controlled with anti-epileptic therapy. As the initial events often occur while the child is sitting before a dish of food, children stop eating adequately, become undernourished, and are often mentally and physically stunted. Affected individuals are more prone to falls and injuries, often bound to their homes, isolated from the rest of the village. They often seem dull and uninterested in their surroundings, presumably due to encephalopathic changes.

An association between *O. volvulus* infection and nodding syndrome has been identified; however, causality still remains unclear. In Tanzania, more than half of the patients with head nodding seizures had glial lesions on magnetic resonance imaging, and the presence of such lesions was associated with positive *O. volvulus* results obtained on PCR testing of skin and/or the CSF. However, they were negative in these patients and there was no major abnormality in other CSF parameters, including the antibody index for *O. volvulus*.[2] Last autumn, the CDC also sent scientists to Uganda to investigate more than 1,000 cases of nodding syndrome that had occurred there. Although the results have yet to be published, agency insiders say the association with the river blindness parasite is similar to that reported from the first South Sudanese community, with a positive association between the worm and the syndrome.[5]

The exact causes and triggers of nodding syndrome remain unclear. Nonetheless, the postulated association with Onchocerca infections can prompt renewed efforts for mass treatment with ivermectin in *O. volvulus*-endemic areas. At the same time, health care infrastructures should be reinforced so that children with seizures and/or encephalopathic changes can gain ready access to good medical care. The CDC is moving ahead with interventional drug trials, assessing the effectiveness of standard anti-seizure drugs as well as high doses of pyridoxine.[5] Further studies and research data are pending, and multi-national collaboration between researchers is crucial in order to uncover the cause of this mystery illness, help affected children, and prevent future cases. ■

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Sarcocystosis in Travelers to Tioman Island, Malaysia

ABSTRACT AND COMMENTARY

By Mary-Louise Scully M.D.

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

Synopsis: *An outbreak of suspected eosinophilic myositis secondary to Sarcocystis is reported in 32 patients who traveled to peninsular Malaysia during the summer of 2011.*

Source: Centers for Disease Control and Prevention. Acute Muscular Sarcocystosis Among Returning Travelers – Tioman Island, Malaysia, 2011. *MMWR* 2012; 61(2):37-38.

In October 2011, GeoSentinel, the global surveillance program of the International Society of Travel Medicine, first reported on the initial findings in probable cases of sarcocystosis among travelers returning from Malaysia. With further investigation, a total of 32 suspected cases of acute muscular sarcocsytosis have now been described. In particular, all of the patients had visited Tioman Island during the summer of 2011. Approximately half of the patients were identified post-travel in Germany; others were from other parts of Europe, North America, and Asia.

All of the patients experienced fever and muscle pain, often prolonged and severe, within days to weeks of returning home. It was noted that all patients had peripheral eosinophilia and many also had elevated serum creatinine phosphokinase levels. Serological tests for trichinosis and toxoplasmosis were negative in all patients tested. One patient (of a group of 5 symptomatic patients who had traveled together) consented to a muscle biopsy,

which demonstrated organisms consistent with sarcocystosis. Similarly, another patient from a group of three that traveled together also had a positive muscle biopsy.

Sarcocystis species are intracellular protozoan parasites classified phylogeneticaly with Babesia, Plasmodium, and Coccidia such as Toxoplasma. More than 100 different species of *Sarcocystis* species exist worldwide and typically have a two-host life cycle based on a prey-predator (intermediate-definitive) host relationship. Humans are the definitive host for *Sarcocystis hominis* and *Sarcocystis suihominis*, acquired through eating undercooked sarcocyst-containing beef or pork, respectively. The resulting infection and sexual reproduction of the parasite in the intestine is often asymptomatic, but it may cause self-limited symptoms of acute gastroenteritis.

Alternatively, humans can serve as intermediate hosts for many of the zoonotic *Sarcocystis* species that are transmitted in nature. In this case, humans ingest oocysts or sporocysts in food or water contaminated with feces from an infected predator animal or reptile. After reproductive and migratory stages, the parasites ultimately disseminate to skeletal, smooth, or cardiac muscle where the formation of sarcocysts cause the classic symptoms of eosinophilic myositis, as seen in this outbreak.

Although there are fewer than 100 reports of human muscular sarcocystosis in the literature it appears that human sarcocystosis is prevalent in Malaysia. A study found sarcocysts in 21% of 100 consecutive autopsy specimens of Malaysians and a seroprevalence study also found evidence of asymptomatic infection in 20% of 243 Malaysians.[1,2]

Histologic examination and DNA amplification are being performed on existing muscle specimens from this outbreak to confirm the diagnosis of muscular sarcocystosis and identify the responsible *Sarcocystis* species.

■ COMMENTARY

Human sarcocystosis cases are unusual, with less than 100 cases reported thus far in the literature. However, this may change with the ever-increasing travel to higher risk areas, such as Malaysia. Tioman Island is a small island off the east coast of Peninsular Malaysia. It is a popular destination for diving and snorkeling, tourists being drawn to the crystal clear blue waters and the variety of tropical fish and marine species. Some of the islands' non-human inhabitants include very large monitor lizards and domestic cats that freely roam the island.

Epidemiologic details on this outbreak are awaited to determine if there was a common source of contaminated food or water exposure. The largest previous outbreak of eosinophilic myositis attributed to Sarcocystis occurred in seven members of a U.S. military team deployed in 1993 to rural peninsular Malaysia for a joint U.S-Malaysian civic action project.[3] Several weeks after returning, the first soldier (index case) reported symptoms of fever, myositis, bronchospasm, fleeting rashes, and eosinophilia. A muscle biopsy of this patient was positive for *Sarcocystis* species. Six out of seven symptomatic patients also had positive serum serology for Sarcocystis. The soldiers were assigned to construct huts and irrigation sluices in a jungle village about 80 km north of Kuala Lumpur. The stay lasted only one week, but it was during seasonal monsoon rains that were particularly heavy that year. The soldiers reported extensive physical contact with the soil, including exposure to both nose and mouth, especially during recreational sporting activities in the ankle deep mud, i.e. "mud wrestling." They also reported having swum in fresh water pools, drinking untreated water, and consuming native foods, including lizard meat. All the patients had mild, self-limited illness except for the index patient who had more serious and chronic sequelae, including possible myocarditis, that appeared to respond to re-treatment with courses of albendazole.

The returning traveler with illness and eosinophilia represents a challenge to travel medicine and infectious disease physicians. Consideration of this as the causative organism in any returning ill patient with myalgia, rash, and eosinophilia is appropriate, especially if the patient is returning from Malaysia. As serology is not readily available, muscle biopsy would seem the most expedient way to make the diagnosis in a suspected case. Any new suspected cases should be reported to the CDC and the corresponding contributor of this report. Although patients often are treated empirically with albendazole and adrenal corticosteroids, there is no known effective treatment or prophylaxis for either intestinal or eosinophilic myositis secondary to Sarcocystis. ■

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US Malaria cases rise, including 9 fatalies

By Lin H. Chen MD

Dr. Chen is Assistant Clinical Professor, Harvard Medical School and Director, Travel Medicine Center, Mt. Auburn Hospital, Cambridge, MA.

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

Synopsis: *Malaria cases in the US rose in 2010, including 9 fatalities. Preventive measures including chemoprophylaxis need to be emphasized especially during popular travel periods to malaria-endemic countries.*

Source: Centers for Disease Control and Preventio. Malaria surveillance – United States, 2010. *MMWR Surveillance Summaries* 2012; 61(2):1-17.

CDC received 1691 reports of malaria diagnosed in the United States in 2010, a 14% increase from 2009, and the highest number of cases since 1980 (n=1864). Among these cases, 1131 were US residents, 368 foreign residents, and 192 had unknown status. Ten percent were classified as severe malaria and 9 patients (8 men and one woman) died; 7% of women diagnosed with malaria were pregnant. One case of malaria was transmitted via transfusion, and the transmission of 2 cases remained unclear.

Overall, the majority of patients had their exposures in Africa (63%), followed by Asia (19%), the Americas (15%), and Oceania (0.4%). Within Africa, West Africa contributed the most cases (73%), with a particularly notable 72% increase of cases acquired in Ghana from 2009. Within Asia, South Asia was the most common region of exposure with 94% of cases, and India was associated with 81% of these. The cases acquired in India increased 57% from 2009. Meanwhile, the Caribbean contributed the most cases in the Americas (77%), and Haiti was the exposure country in 96%, which represented a 66% increase from 2009. Nigeria, Haiti, and Ghana were the leaders, followed by Sierra Leone and Liberia, Cotes d'Ivoire, and Cameroon.

US residents most frequently acquired malaria in Africa. While this was also true for foreign visitors, Asia contributed a higher proportion to the region of exposure in foreigners. A few areas reported the majority of malaria cases: New York City, Florida, California, New Jersey, Texas, and Maryland. The most commonly reported reason for travel for US residents was to visit friends and relatives [VFR - 54%], followed by missionary activities (7%) and business (6%). The highest proportion was in persons aged 18-64 years, and 15% were in children <18 years of age and 5% in persons >65 years of age.

The species identification improved from what was reported in 2009. Among 1388 cases that had the causative species identified, *Plasmodium falciparum* remained the most common species (71%), followed by *P. vivax* (23%). Where the species and the region of exposure were reported, *P. falciparum* caused 86% of infections acquired in Africa, 81% in the Americas, 9% in Asia, and 40% in Oceania. *P. vivax* caused 6% of infections from Africa, 16% from the Americas, 87% in Asia, and 60% in Oceania.

The timing of the US cases peaked in January and July among patients who reported travel to Africa, associated with the winter and summer breaks in the US. The cases to Asia peaked in August with a smaller peak in November. For cases with known dates of arrival in the US and onset of illness, 11% had symptom onset before arrival, and the remainder mostly occurred within 1 month of arrival (84% of *P. falciparum* and 59% of *P. vivax* cases).

Analysis of chemoprophylaxis used among the US residents showed that about 25% took chemoprophylaxis, but 16% of those who specified a drug had taken one that was not recommended by CDC for their destinations. Sixty percent had missed doses among those who took recommended medications. Among those who took recommended chemoprophylaxis and had species identified (n=120), *P. vivax* and *P. ovale* accounted for 18% (n=22) and 8% (n=10), respectively, and included 12 cases that were considered relapses, rather than primary chemoprophylaxis failure, since they occurred >45 days after arrival to the US. Only 2 patients reported adherence, and had traveled to Africa and India taking mefloquine and atovaquone/proguanil, respectively. Six of the patients considered to have relapses received primaquine for anti-relapse therapy.

Among the failures with *P. falciparum* (n=80), nearly all were acquired in Africa or Haiti. Those that adhered to chemoprophylaxis (n=19) included 14 that traveled to Africa while taking mefloquine (n=7), doxycycline (n=5), and atovaquone/proguanil (n=2); 3 took chloroquine (n=2) or doxycycline (n=1) for travel to Haiti. All patients diagnosed with *P. malariae* who reported adherence (n=3) had exposures in Africa. Two took mefloquine and one took atovaquone/proguanil for chemoprophylaxis.

Treatment in uncomplicated cases was appropriate in 87% but inappropriate in 13%. The inappropriate treatments included using the same drug as that utilized for chemoprophylaxis. Less than half of the *P. vivax* and *P. ovale* patients received primaquine for anti-relapse therapy.

■ COMMENTARY

The increase in malaria cases in 2010 is of concern, including the significant increase in pregnant women. Most of the fatalities occurred in persons who did not take malaria chemoprophylaxis, or used non-recommended regimens obtained abroad. West Africa remains the high-risk region, and Nigeria, Ghana, Sierra Leone and Liberia, Cotes d'Ivoire, and Cameroon continued to top the list. A

TABLE 5. Number and percentage of imported malaria cases, by interval between date of arrival in the United States and onset of illness and *Plasmodium* species* — United States, 2010

	P. falciparum		*P. vivax*		*P. malariae*		*P. ovale*		Mixed		Total	
Interval (days)	No.	(%)	No.	(%)	No.	(%)	No	(%)	No	(%)	No.	(%)
<0†	82	(10.9)	24	(12.2)	2	(8.0)	1	(5.3)	0	(0.0)	109	(10.9)
0–29	632	(83.8)	117	(59.4)	15	(60.0)	7	(36.8)	8	(100.0)	779	(77.7)
30–89	29	(3.9)	24	(12.2)	7	(28.0)	3	(15.8)	0	(0.0)	63	(6.3)
90–179	5	(0.7)	21	(10.6)	1	(4.0)	6	(31.5)	0	(0.0)	33	(3.3)
180–364	5	(0.7)	11	(5.6)	0	(0.0)	1	(5.3)	0	(0.0)	17	(1.7)
>365	0	(0.0)	0	(0.0)	0	(0.0)	1	(5.3)	0	(0.0)	1	(0.1)
Total	753	(100.0)	197	(100.0)	25	(100.0)	19	(100.0)	8	(100.0)	1,002	(100.0)

* Persons for whom *Plasmodium* species, date of arrival in the United States, or date of onset of illness is unknown are not included.
† Cases in this row are in patients who had onset of illness before arriving in the United States.

dramatic increase (66%) in the total number of infections acquired in Haiti, and the cases among humanitarian workers there, illustrated probable intensified transmission as well as increased travel volume.[1] Business travel appears to have emerged in importance as a cause of malaria alongside missionary travel, and business travelers should be advised appropriately.

The increase in pregnant travelers diagnosed with malaria is also worrisome. Most (83%) appeared to be VFRs, and prevention messages should aim for communities with high proportions of VFR travelers. If travel to malaria-endemic regions is unavoidable during pregnancy, mefloquine and chloroquine are recommended for chemoprophylaxis depending on parasite resistance. Of note, the USFDA changed mefloquine to a pregnancy category B drug, from category C, in 2011, endorsing its safety during all trimesters of pregnancy.[2] Similarly, the peak incidences of malaria cases suggest the need for malaria prevention messages to target the popular travel seasons of winter holiday and summer vacations.

For a number of years, the most commonly reported reason for travel in patients diagnosed with malaria has been VFR. The year 2010 was no exception. Nearly half the cases in those <18 years old were children of foreign-born parents, indicating a group with significant risk that should receive focused malaria prevention education.[3]

The same regions within the US continue to report the highest numbers of malaria cases. These areas correspond to the presence of high population concentrations including foreign-born persons, high levels of travel, and are near major airline hubs for international flights;[4] therefore physicians in those areas should be well-trained in recognizing malaria risk and in the appropriate diagnosis and treatment.

P. falciparum remained the leading malaria species in Africa while *P. vivax* predominates in Asia and Oceania. However, *P. vivax* should not be neglected in the consideration of febrile travelers returning from Africa since it causes 1/16 of all malaria cases.

This surveillance found that the majority of malaria cases occurred within 1 month of arrival, which concurs with earlier data. However, significant proportions of *P. vivax* and *P. ovale* occurred beyond 3 months after return (16% and 42%, respectively), including a case of *P. ovale* that occurred >1 year after return. (*See table, this page*.) Therefore, the diagnosis should still be considered long after exposure.

Although a few cases of chemoprophylaxis failure occurred, the analysis showed that most of the malaria cases did not take appropriate recommended chemoprophylaxis or were not adherent. Unfortunately, these cases might have been prevented if the patients had adhered to chemoprophylaxis. Even more tragic were the fatal cases for which chemoprophylaxis was neglected, mostly for travel to high-risk countries in West Africa.

Malaria treatment also needs improvement. Although a high proportion received appropriate treatment, those treated with the same drug as they had taken for chemoprophylaxis potentially confront resistant parasites that could have devastating outcomes. For severe malaria, intravenous artesunate achieves better parasite clearance and fever resolution than other malaria treatment regimens.[5, 6] Artesunate is available through CDC by contacting the Malaria Hotline: 1-770-488-7788, 1-855-856-4713, or 1-770-488-7100. The CDC Malaria website for treatment assistance is: www.cdc.gov/malaria. ■

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CME Questions

1. Which of the following is NOT a described means of transmission of Trypanosoma cruzi, the parasitic agent which causes Chagas disease?
   A. Vector-borne (triatomine insects)
   B. Blood transfusion
   C. Oral/ingestion
   D. Respiratory / inhalation
   E. Congenitally (from mother-to-child)

2. Nodding syndrome is:
   A. A result of rheumatic fever – induced aortic valve disease with pulsatile head-bobbing
   B. A poorly understood trauma-associated seizure disorder in rural southeastern Asia
   C. An incompletely characterized childhood epilepsy associated with onchocerciasis.
   D. A form of congenital epilepsy found in children of consanguineous marriages

3. Which one of the following statements is true about human infection with Sarcocystis?
   A. Humans cannot serve as intermediate hosts.
   B. Effective anti-parasitic agents for treatment are available.
   C. Human sarcocystosis infection is almost always associated with clinical illness.
   D. Rapid antigen testing is available for diagnosis when necessary to dictate therapy.
   E. Human muscular sarcocystosis can be acquired by eating undercooked infected beef or pork.

CME Objectives & Instructions

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

- discuss the latest data regarding the diagnosis and treatment of various travel-related diseases;
- explain new data concerning recommended precautions and prophylaxis for patients traveling to specific areas of the world;
- implement strategies in the practice setting to inform patients of disease outbreaks and epidemics relevant to their travel plans.

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

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

Critical Drug Shortages Are on the Rise

In this issue: Drug shortages; metformin and cancer prevention; migraine prevention guidelines; and FDA actions.

What's causing the shortages?

Drug shortages are happening at an unprecedented rate. Just in the last 2 months, we have seen shortages of diazepam, methotrexate, leucovorin, naltrexone, oxymorphone, mitomycin, fentanyl, metoclopramide, pantoprazole, ondansetron, and dexamethasone among others. What is causing the shortages and is there any end in sight? Although it seems like a new problem, we have seen an increasing number of drug shortages going back to 2005. But while there were about 50 drug shortages in the mid 2000s, last year more than 260 drugs were in short supply, including many commonly used and clinically vital drugs. The cause of these shortages is multifactorial. Some sources in the industry blame price controls, especially for generic drugs. Medicare and Medicaid impose strict controls on most generics, squeezing pharmaceutical companies' ability to make a profit. Some companies have simply decided to drop out of the generic market altogether. Others blame fewer manufacturers. The *Wall Street Journal* reports that there were 26 vaccine makers in the United States in 1967, while currently there are only six. But even these issues do not explain the severe shortages we are seeing. Most experts agree the two major issues causing the current shortages are supply chain disruptions, especially disruptions in raw materials, and problems with manufacturing, especially safety issues, which force the FDA to shut down production of a product line or an entire factory. Safety shutdowns are the most common cause of shortages of sterile injectable drugs. But in other cases, companies limit production themselves when they either have an absolute shortage of raw materials or they decide to divert limited supplies of raw materials from less expensive generics to more expensive brand-name drugs. This is a current issue with some of the attention deficit hyperactivity disorder drugs that have been in short supply for several months. Last month, the FDA initiated a series of steps to increase the supply of critically needed cancer drugs, including allowing the importation of drugs in shortage from Europe and elsewhere. The agency is also fast tracking approval of new manufacturers for short-supply drugs like methotrexate. The FDA, as well as the Obama administration, is also requiring companies to give early warning of potential drug shortages. Finally, the Justice Department will aggressively pursue possible incidences of collusion or price gouging among drug distributors who may be taking advantage of shortages. Despite these steps, there will likely be no short-term easing in drug shortages. ■

Does metformin prevent cancer?

Last month, we reported that low-dose aspirin may be protective against some cancers. Now it looks like metformin may have similar properties. A new study from the American Association for Cancer Research suggests that the diabetes drug may improve the prognosis with pancreatic cancer. In a retrospective study, researchers at the University of Texas studied 302 patients with diabetes and

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pancreatic cancer; 117 of these patients were taking metformin. The 2-year survival rate was 30.1% for the metformin group vs 15.4% for the non-metformin group ($P = 0.004$; x^2 test). The pancreatic cancer patients on metformin lived 4 months longer than non-metformin patients (15.2 months vs 11.1 months). The authors suggest that metformin should be evaluated as a supplemental therapy for patients with pancreatic cancer (*Clin Cancer Res* published online March 31, 2012; doi: 10.1158/1078-0432.CCR-11-2994). Data presented at the AACR meeting in Chicago earlier this year suggest that the drug may also be beneficial for men with prostate cancer, although further research is needed. ■

Migraine prevention in adults

The American Academy of Neurology and the American Headache Society have published their new guideline on pharmacologic treatment for episodic migraine prevention in adults. The highest level (Level A) recommendation for prevention was given to antiepileptic drugs, including divalproex sodium, sodium valproate, and topiramate. Other level A drugs included the beta-blockers metoprolol, propranolol, and timolol as well as the triptan frovatriptan, but this last agent is just for short-term use for menstrually associated migraine (MAM) prevention. Level B drugs included the antidepressants amitriptyline and venlafaxine, the beta-blockers atenolol and nadolol, and the triptans naratriptan and zolmitriptan (also only for short-term MAM prevention). Possibly effective medications included lisinopril, candesartan, some beta-blockers, and carbamazepine. There was little or no evidence to support any other drugs including selective serotonin reuptake inhibitors, calcium channel blockers, or acetazolamide. Drugs that should not be offered include lamotrigine and clomipramine. In a separate section on nonsteroidal anti-inflammatory drugs (NSAIDs) and complementary treatments, Petasites hybridus (butterbur) were given recommended status, while NSAIDs were listed as probably effective (*Neurology* published online April 24, 2012; doi: 10.1212/WNL.0b013e3182535d20, and doi: 10.1212/WNL.0b013e3182535d0). ■

Fibrate use in elderly patients

Fibrate use in elderly patients is associated with worsening renal function and increased risk of hospitalization, according to a new study. Researchers reviewed data from a large Canadian database of patients over the age of 65 who were started on a fibrate or ezetimibe (comparator). Many patients in both groups were also on statins. Fibrate users were more likely to be hospitalized for an increase in serum creatinine (odds ratio [OR] 2.4 [95% confidence interval (CI), 1.7 to 3.3]). Fibrate patients were also more likely to consult a nephrologist, but there was no difference in all-cause mortality or need for dialysis. In a subgroup of 1110 patients in which serum creatinines were available at baseline and within 90 days, 9.1% of fibrate users and 0.3% of ezetimibe users had an increase in serum creatinine of 50% or more (OR 29.6 [CI, 8.7 to 100.5]). The risk was higher if patients had chronic kidney disease. The authors conclude that new fibrate use in the elderly is associated with an increase in serum creatinine and a small increase in hospitalization and nephrology consultation (*Ann Intern Med* 2012;156:560-569). ■

FDA actions

The FDA has approved the first PDE5 inhibitor in a decade for the treatment of erectile dysfunction (ED). Avanafil (Stendra) joins sildenafil (Viagra), tadalafil (Cialis), and vardenafil (Levitra) as the fourth drug approved for this indication. Avanafil will be marketed as having a shorter onset and a shorter half-life than the other drugs in this class. Men should take avanafil as needed 30 minutes before sexual activity with onset of action as quickly as 15 minutes. The approval was based on three randomized, placebo-controlled clinical trials of 1267 patients with ED in which 57% of men achieved erections sufficient for intercourse, up from a baseline of 15% (compared to 27% with placebo). Like other PDE5 inhibitors, avanafil should not be taken with nitrates. Commonly reported side effects include headache, flushing, nasal congestion, nasopharyngitis, and back pain. Avanafil will be marketed by VIVUS of Mountain View, California, as Stendra.

The FDA is requiring new labeling on finasteride — Merck's testosterone blocker used for the treatment of benign prostatic hypertrophy (5 mg as Proscar) and male pattern baldness (1 mg as Propecia). The new labeling addresses sexual adverse events such as libido disorders, ejaculation disorders, orgasm disorders, and even male infertility and poor semen quality. Some of these issues, such as libido disorders and ejaculation disorders, may continue after stopping the drug, while infertility and poor semen quality improve or normalize after discontinuation. The labeling change is based on event reports filed with the FDA, although a clear causal relationship has not been made. Still, the agency is recommending that a discussion of the risks and benefits of finasteride include the possibility of sexual side effects. ■