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Guillain-Barré Syndrome and Menactra Meningococcal Conjugate Vaccine

ABSTRACT & COMMENTARY

By Mary-Louise Scully
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Dr. Scully reports no consultant, stockholder, speaker's bureau, research, or other financial relationship with any company having ties to this field of study.

Synopsis: *As of October 4, 2005, the Vaccine Adverse Event Reporting System (VAERS) received five reports of Guillain-Barré syndrome after receipt of Menactra® vaccination. Although the rate of Guillain-Barré after vaccination is similar to what might be expected by chance alone, the timing of the onset of symptoms within 2 to 5 weeks after vaccination prompted the dispatch to alert physicians to report any additional cases.*

Source: Guillain-Barré Syndrome Among Recipients of Menactra Meningococcal Conjugate Vaccine- United States, June-July 2005. *MMWR Morb Mortal Wkly Rep*. 2005;54:1023-1025.

MENACTRA, A QUADRIVALENT (A, C, Y, AND W135) MENINGOCOCCAL CONJUGATE vaccine (MCV4), was licensed in the United States on January 14, 2005. Each 0.5mL dose of MCV4 contains 4g of each capsular polysaccharide from *Neisseria meningitidis* serogroups A, C, Y, and W135 conjugated to 48g of diphtheria toxoid. In February 2005, the Advisory Committee on Immunization Practices (ACIP) recommended that in addition to the previous recommendations for first-year college students living in dormitories and other high-risk groups, MCV4 can be given at the preadolescent visit (ages 11-12 years) or prior to high school at 15 years if not previously vaccinated. The manufacturer distributed approximately 2.5 million doses nationally since March of 2005, though the exact number of vaccine doses actually administered is not known.

All 5 patients reported with Guillain-Barré Syndrome (GBS) were between the ages of 17-18 years and were vaccinated between June 10, 2005 and July 25, 2005. A sixth case was reported to be under investigation. The 5 cases were reported from Pennsylvania (2 cases), New York, Ohio, and New Jersey (one case each), and from 4 different vaccine lots. Each of the cases had onset of symptoms within 14-31 days after vaccination with MCV4. All 5 cases were hospitalized with compatible clinical findings of GBS, and 4 of the 5 cases had nerve conduction testing consistent with GBS.

The most severe case was an 18-year-old female who had paralysis of her arms, difficulty swallowing, and progressive respiratory compromise requiring

mechanical ventilation. She was treated with IVIG and plasmapheresis. This patient was transferred to a rehabilitation facility and did improve to the point of being able to talk, sit, stand, and feed herself, 53 days after the onset of her GBS.

One case is notable in that the patient had a history of 2 previous cases of GBS after childhood vaccinations at ages 2 and 5 years. Although reduced or absent ankle, knee, and arm reflexes were noted on physical exam, no nerve conduction studies appear to have been done on this patient. The CSF analysis revealed 0 WBC/mm^3 and a protein of 26 mg/dL. She was treated with IVIG, recovered, and was discharged home.

Treatment with either plasmapheresis in one case, with IVIG in 3 cases, or both plasmapheresis plus IVIG in one case was given. Only one case had an acute illness, sore throat, before the onset of neurologic symptoms. In particular, no patients reported symptoms of a bacterial gastroenteritis suggestive of *Campylobacter jejuni*, which has previously been identified as a precipitating factor for GBS.

No cases of GBS had been reported in the 7000 recipients of MCV4 prior to licensure of the vaccine.[1] In addition, a rapid survey conducted by the CDC Vaccine Safety Datalink and other healthcare organization databases did not detect any cases of GBS in 110,000 recipients of MCV4. Data on GBS incidence in persons aged 11-19 years indicate a possible annual incidence of 1-2 cases per 100,000 years.[2] This might suggest that the number of cases reported within 6 weeks of administration of MCV4 is not increased from the number expected to occur by chance alone. However, the fact that the onset of neurologic symptoms did occur within 2-5 weeks after vaccination with MCV4 prompted the dispatch to increase awareness of a possible association.

COMMENTARY

GBS is an acute idiopathic inflammatory demyelinating peripheral neuropathy that is characterized by progressive, symmetrical muscle weakness and areflexia. It is usually associated with spontaneous remission. In the past, GBS was thought of as a single disorder, but now is felt to consist of at least 4 subtypes: acute inflammatory demyelinating polyneuropathy (AIDP), acute motor axonal neuropathy (AMAN), acute motor and sensory axonal neuropathy (AMSAN), and the Miller Fisher variant (MFS). The AIDP subtype is the most common and resembles experimental autoimmune neuritis with immune mediated damage directed against peptides from the myelin proteins. The axonal subtypes, AMAN and AMSAN, are likely caused by antibodies to gangliosides that target macrophages to invade the axon at the node of Ranvier.

It is estimated that 25% of patients with GBS have had a recent *Campylobacter jejuni* infection, and these patients more often have axonal forms of GBS. Research has shown that the lipo-oligosaccharide from the *C. jejuni* bacterial wall contains ganglioside-like structures that, when injected into rabbits, induce an acute motor axonal type neuropathy.[3] GBS has been thought to be associated with a variety of systemic and infectious processes, but many reports are anecdotal. One case control study of 308 GBS patients did find serologic evidence of recent infection with Campylobacter, cytomegalovirus, or Epstein-Barr virus.[4] No illness, viral or bacterial, seemed to pre-date the onset of

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neurologic symptoms in 4 out of the 5 GBS cases.

Concerns that immunizations might trigger GBS in susceptible persons are not new. In particular, the swine flu vaccine of 1976 was associated with a slightly increased incidence of GBS. When data on GBS reported for the 1992-1993 and 1993-1994 influenza seasons were combined, it was found that influenza vaccination resulted in approximately one additional case of GBS per million doses given.[5] This GBS risk is much less than the risk of severe influenza. Despite many individual case reports, other conventional vaccines are not felt to be associated with an increased risk of GBS except, perhaps, brain-derived rabies vaccine, which is not available in the United States and may be followed by GBS in about one in 1000 recipients.[6] Information on whether other vaccines, such as a tetanus-diphtheria booster, were given at the same time as the MCV4 vaccine in these 5 GBS patients, was not provided in the report.

Meningococcal meningitis affects approximately 2600 people each year in the United States. Physicians and the lay public respect and fear this illness that often affects young, previously healthy patients, with a peak in the United States in 17-18-year-olds. Mortality can be 15-25%, despite treatment with appropriate antibiotics. Those that do survive can be left with significant, permanent neurologic deficits. The addition of MCV4 vaccine in the battle to combat this devastating illness was welcomed by healthcare providers, and this report of a possible GBS association was indeed sobering. The current information is very preliminary, and the FDA and CDC are continuing to evaluate the issue and are asking that providers report any GBS or other significant adverse events after MCV4 to VAERS at www.vaers.hhs.gov or by phone at 800-822-7967. Also, providers are urged to report any case of GBS that occurs in any patient aged 11-19 years in accordance with state or local disease-reporting guidelines.

There has been no change in the recommendations for meningococcal vaccination, and the Vaccine Information Statement has been updated October 7, 2005, with the GBS information (www.cdc.gov/nip/publications/VIS/default.htm). MCV4 is only approved for patients between ages 11-55. The older meningococcal polysaccharide (MPSV4) vaccine remains available and is the recommended option for children 2-10 years old and adults over 55 who are at increased risk of meningococcal disease or traveling to areas of the world where meningococcal disease is common, such as Sub-Saharan Africa. ■

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Hurricane Katrina: Infectious Disease Issues

ABSTRACT AND COMMENTARY

By Lin H. Chen MD

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Dr. Chen reports no consultant, stockholder, speaker's bureau, research, or other financial relationship with any company having ties to this field of study.

Synopsis: *Wound infections from Vibrio vulnificus and Vibrio parahaemolyticus were diagnosed in evacuees from areas devastated by Hurricane Katrina. The increased occurrence of Vibrio infections illustrates an infectious disease risk from exposure to flood water, especially in persons with chronic disease.*

Sources: CDC. Vibrio Illnesses After Hurricane Katrina—Multiple States, August-September 2005. *MMWR Morb Mortal Wkly Rep*. 2005;54:928-931; CDC. Infectious Disease and Dermatologic Conditions in Evacuees and Rescue Workers After Hurricane Katrina—Multiple States, August-September, 2005. *MMWR Morb Mortal Wkly Rep*. 2005;54:961-964.

HURRICANE KATRINA STRUCK THE US GULF COAST ON August 29, 2005, and led to a disaster involving multiple states, particularly Louisiana, Mississippi, and Alabama. Surveillance of illnesses during the 2 weeks following Hurricane Katrina identified 22 Vibrio infections in residents or evacuees from Louisiana, Mississippi, and Alabama. Eighteen of these were wound infections: 14 *V. vulnificus*, 3 *V. parahaemolyticus*, and one was not speciated. Five patients with Vibrio wound infections

died: 3 with *V. vulnificus*, 2 with *V. parahaemolyticus*. Age of patients ranged from 31 to 89 years, and 15 (83%) were male. Thirteen of the patients had underlying conditions including heart disease, diabetes mellitus, renal disease, alcoholism, liver disease, peptic ulcer disease, immunodeficiency, and malignancy.

Four patients were reported to have non-wound-associated Vibrio infections. Two of the patients had gastroenteritis and nontoxigenic *V. cholerae* (non-01, non-0139) was identified, but speciation in the other 2 patients was not reported. The Gulf States reported 11-18 cases of noncholeragenic Vibrio infections during the month of September from 2000 to 2004, including 4-8 cases of wound infections. Therefore, Vibrio gastrointestinal disease did not appear to have increased after Hurricane Katrina. However, the 18 wound-associated Vibrio infections represent a clear increased incidence, and occurred in patients who had exposure to flood water.

By the end of September, 24 cases of *V. vulnificus* and *V. parahaemolyticus* wound infections were reported among evacuees, with 6 deaths. Surveillance also found methicillin-resistant *Staphylococcus aureus* in 30 evacuees from the New Orleans area at a facility in Dallas, Texas. Clusters of diarrheal diseases were reported, and identified norovirus and nontyphoidal Salmonella, in addition to nontoxigenic *V. cholerae* 01. Respiratory diseases reported include pertussis, tuberculosis, streptococcal pharyngitis, and respiratory syncytial virus. Additionally, about 200 cases of presumed viral conjunctivitis were reported in evacuees. Among rescue workers, tinea corporis, folliculitis, arthropod bites (likely mite bites), and prickly heat were reported.

COMMENTARY

Vibrio vulnificus is a Gram-negative rod described as a "halophilic (salt-requiring) Vibrio", and has been recognized as a marine organism associated with wounds and consumption of raw oysters.[1] The organism is present in temperate estuarine and coastal waters, especially when water temperatures are > 20 C.[2] Most cases occur in the warm season, usually from May to October.[1] Infection can present as wound infection, gastroenteritis, or primary septicemia. In wound-associated infections, symptoms usually begin within 4 hours to 4 days with swelling, erythema, and pain. The wounds progress rapidly into cellulitis, vesicles, or bullae, and can necrose; other signs and symptoms include fever, chills, mental status changes, ecchymosis, hypotension, diarrhea, vomiting.[2,3] In one study from Florida, the median age of patients with wound-associated *V. vulnificus* infections was 61 years, with a male predominance; case fatality rate was 24%.[2] Individuals with underlying chronic diseases, such as liver disease, diabetes, alcoholism, congestive heart failure, and malignancy appear to be more susceptible to developing septicemia with *V. vulnificus*.[1-3] *V. vulnificus* septicemias are associated with the ingestion of raw or contaminated seafood, and infection can also manifest as osteomyelitis, pneumonia, endometritis, fallopian tube infections, or corneal ulcerations.[3] A tetracycline antibiotic is considered the drug of choice for *V. vulnificus* infection, although cefotaxime, ciprofloxacin, chloramphenicol, and gentamicin may also be effective; early treatment greatly improves outcome.[2]

Similar to *V. vulnificus*, *V. parahaemolyticus* is also a marine pathogen, occurring after exposure to seawater, with warm-season predominance. The epidemiology of Vibrio infections in Florida from 1981 to 1993, showed that *V. parahaemolyticus* and *V. vulnificus* were the leading Vibrio species causing wound infections.[2,4] *V. vulnificus* was the most frequent Vibrio species associated with primary septicemia, whereas *V. parahaemolyticus* was the most common Vibrio species to be associated with gastroenteritis.[4] In addition, *V. parahaemolyticus* is the most common cause of seafood-associated gastroenteritis in the United States, recently implicated in an outbreak following consumption of Alaskan oysters.[5]

In comparison, the tsunami that devastated southern Asia on December 26, 2004, also led to many cases of wound infections. Interestingly, Aeromonas species, organisms associated with fresh or brackish water, were the most commonly identified organisms in skin and soft-tissue infections among survivors in southern Thailand.[6] Among the total of 641 isolates identified, 145 were Aeromonas species compared to 10 Vibrio species (7 *V. parahaemolyticus*, 2 *V. vulnificus*, 1 *V. alginolyticus*).[6]

A norovirus outbreak was also associated with Hurricane Katrina. From September 2-12, 18% of 6500 evacuees that visited the Reliant Park medical clinic in Houston, Texas, reported acute gastroenteritis.[7] Acute gastroenteritis reported in medical personnel, police, and volunteers who had direct contact with patients led to suspicion of secondary spread. Norovirus was found in 50% of stool samples tested by reverse transcription-polymerase chain reaction; approximately 1000 evacuees and relief workers in the Houston area may have been affected.[7] The norovirus outbreak highlights transmission of this virus in environments with crowding and with suboptimal sanitation.

Finally, carbon monoxide poisoning is an additional health hazard that occurred in Alabama, Louisiana, and Mississippi after Hurricane Katrina.[8] The predominant cause was exposure to exhaust from portable generators, and could have been prevented by appropriate ventilation of the generators. ■

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Sushi Delights and Parasites: The Risk of Fishborne and Foodborne Parasitic Zoonoses in Asia

By Michele Barry, MD, FACP

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Dr. Barry is a consultant for the Ford Foundation, and receives funds from Johnson & Johnson.

Synopsis: *Because of worldwide popularization of Japanese cuisine, travelers who consume sushi and sashimi in countries where certain zoonoses are endemic, and prefreezing is an uncommon practice, may put themselves at risk for infection. Sushi and sashimi prepared without flash freezing can put the traveler at risk for exotic fishborne parasites. Undercooked wild animal meats also served as sushi and sashimi overseas can also become sources of zoonotic parasites. This review provides practical background information with an excellent table of endemic regions.*

Source: Nawa Y, et al. Sushi Delights and Parasites: The Risk of Fishborne and Foodborne Parasitic Zoonoses in Asia. *Clin Infect Dis*. 2005;41:1297-303

A REVIEW OF THE POTENTIAL PARASITES TRAVELERS might acquire by eating traditional Japanese sushi (rice with raw fish wrapped in seaweed) or sashimi (thinly sliced raw fish) was reviewed in CID by Nawa and colleagues. Due to FDA recommendations, most expensive marine fish served in US restaurants have been frozen at less than -35°C for 15 hours, or at less than -20°C for 7 days and, thus, pose a very low risk of infection. Fortunately, the commonly served tuna, yellow tail, snapper, salmon, and flatfish/flounder rarely carry parasites; other than salmon, which may harbor *Diphyllobothrium latum*. Cheaper marine fish such as cod, herring, mackerel, or squid could transmit *Anisakis larvae*. In rural areas in Japan, various other animals (crabs, snails, frog, boar, bovine liver) are consumed raw or undercooked and served as sushi or sashimi, especially in the mountainous areas. This review provides practical information regarding fishborne parasites acquired in Asia.

Anisakiasis incidence in Japan has felt to be increasingly due to enhanced detection by endoscopy. These larvae usually cause acute abdominal pain within a few minutes after consumption of infected fish to several hours after they penetrate the gastric wall. Rarely, they can penetrate the intestine and migrate to other organs. An antigen-capture ELISA with reported sensitivity and specificity of near 100%; eosinophilia and/or endoscopy can clinch the diagnosis once an immune response has developed.

Diphyllobothriasis infection is spreading in Japan due to commonly served lake trout and salmon, with > 100 cases described annually from the north. Detection of the tapeworm is usually based on ova or proglottids being found in the feces. Megaloblastic anemia is rarely seen.

Gnathostomiasis is mainly contracted by consumers of sashimi in Thailand and Japan—although a recent outbreak occurred in Latin America. Various fish harbor the parasite: tiny squid, snakehead, catfish, tilapia, brook trout, and sashimi of terrestrial snakes have been implicated. Migratory erythema, serpiginous eruptions, and dramatic eosinophilia are common symptoms. Occasionally, serious neurological illness can present as eosinophilic meningoencephalitis, radiculitis, and subarachnoidal bleeding; less commonly migration to other organs can occur.

Intestinal capillariasis is endemic in the Philippines and Thailand, but sporadic cases occur in Japan, Korea, Taiwan, India, Iran, Indonesia, and Egypt. Freshwater and brackish-water fish have been implicated, and patients will experience diarrhea and abdominal pain. Characteristic ova are passed in stool samples.

Table 1

Fishborne and Other Foodborne Parasites

			Site(s) of infection	
Parasites	**Source of human infection**	**Area with edemicity**	**Usual**	**Occasional**
Anisakis simplex	Marine fish (herring and mackarel)	Cosmopolitan regions	Stomach	Intestine and peritoneal cavity
Pseudoterranova decipiens	Marine fish (cod and squid)	Cosmopolitan regions	Stomach	
Diphyllobothrium latum[a]	Lake trout	Cosmopolitan regions	Intestine	
Gnathostoma sp.	Freshwater fish and snakes	Asia, Latin America, and Africa	Skin	Eyes and CNS
Capillaria philippinenis	Freshwater and brackish-water fish	The Phillipines and Thailand		Intestine
Clonorchis sinensis	Freshwater and brackish-water fish	East Asia	Liver	
Opistorchis viverrini	Freshwater fish	Indochina	Liver	
Minute intestinal flukes				
Metagonimus yokogawai	Freshwater fish	Japan and Korea	Intestine	
Others	Freshwater fish, frogs, and snakes	Asia	Intestine	
Paragonimus species	Freshwater crabs, crayfish, and wild boar	East Asia	Lung	Skin and CNS
Angiostrongylus cantonensis	Snails, slugs, and green vegetables	Pacific Islands, Taiwan, and China	CNS	
Spirometra erinaceieurpaei	Snakes, frogs, and backyard chicken	Cosmopolitan regions (mainly in Asia)	Liver	
Fasciola hepatica[b]	Aquatic plants and bovine liver	Cosmopolitan regions	Liver	
Fasciolopsis buski	Aquatic plants	China, Indochina, and India	Intestine	

[a] The species endemic in Japan is classified as *Diphyllobothrium nihonkaienze*, and the major source of infection is an ocean trout.

[b] The species endemic in Asia is classified as *Fasciola gigantica*.

Paragonimiasis westermani causes human disease, especially in Asia, after ingestion of infected freshwater crabs. Fever, chest pain, hemoptysis, and lung lesions mimicking cavitary tuberculosis indicate disease. Ectopic migration can occur, causing extrapulmonary symptoms; cutaneous and cerebral diseases have been described. Diagnosis is confirmed by detection of ova in sputum, stool, biopsies, or serologic testing.

Several species of liver flukes, *Clonorchis sinensis*, and *Opisthorchis viverrini* are known to cause hepatobiliary disease in southeast Asia. Human infection occurs after eating raw freshwater or brackish water fish carrying infective larvae. Heavy infection can lead to jaundice, liver cirrhosis, and cholangiocarcinoma. Another important liver fluke infection caused by *Fasciola hepatica* can result from ingesting aquatic plants or sashimi of bovine liver—a delicacy in Yakitori bars in Japan. Intestinal flukes (*Metagonimus yokogawi*) are a well-known sequelae of eating the famous freshwater fish Ayu in Japan. Eating raw snails, slugs, or green salads may precipitate angiostrongyliasis—a cause of eosinophilic meningitis.

Sparganosis or spirometrosis occurs when sashimi of infected frogs or snakes are ingested. Approximately 500 cases have been reported in Japan. Larvae usually appear in the subcutaneous tissues as slow-growing migratory nodular lesions. Occasional CNS lesions occur. *Table 1* in the paper outlines those areas with parasite endemicity.

Neurotoxicity: The Risk of Malaria Misdiagnosed and Treated

ABSTRACT AND COMMENTARY

By Maria D. Mileno, MD

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Dr. Mileno is a consultant for GlaxoSmithKline, and is involved in research with Merck.

Synopsis: *Readers are alerted to a case report published in Clinical Infectious Diseases which illustrates the degree of potential toxicity that could occur with use of antimalarial medications. In this case the malaria was also misdiagnosed.*

Source: Franco-Paredes C, et al. Neurotoxicity Due to Antimalarial Therapy Associated with Misdiagnosis of Malaria. *Clin Infect Dis*. 2005;40:1710-1711.

A 39-YEAR-OLD MAN WHO TRAVELED TO SIERRA Leone presented with tremors, lack of coordination, poor concentration, and severe anxiety upon return to the United States. He received treatment for

Table 2

Safety and Tolerability of Available Antimalarial Drugs

Drug	Adverse Effects	Contraindications	Severe Adverse Events
Chloroquine	Gastrointestinal upset, itching, and dizziness	Epilepsy	Death from overdose
Sulfadoxine-pyrimethamine		Pregnancy , renal disease	Stevens-Johnson syndrome
Quinine	Tinnitus, vertigo, headache, fever, syncope,	G6PD deficiency, pregnancy,	Hemolytic anemia, coma, respirato-
ry			
	delirium, nausea	optic neuritis, tinnitus, thrombocytopenic purpura, blackwater fever	arrest, renal failure
Mefloquine	Vomiting, headache, insomnia, vivid dreams anxiety, dizziness	Depression, schizophrenia, anxiety disorder any psychosis, irregular heartbeat	Psychosis
Atovaquone-chloroguanide	Gastrointestinal upset, headache, stomatitis	Weight < 11 kg in children, pregnancy, breast-feeding, renal impairment	None known
Artemther-lumefantrine	Dizziness, palpitations	Pregnancy, severe malaria	Impaired hearing
Artesunate-mefloquine	Vomiting, anorexia, diarrhea	Depression, schizophrenia, anxiety disorder any psychosis, irregular heartbeat	None known
Halofantrine	Gastrointestinal upset, prolonged QTc	Conduction abnormalities, pregnancy, breast-feeding, infancy, use of mefloquine	Cardiac arrest
Primaquine	Gastrointestinal upset, elevated levels of methemoglobin	Pregnancy, G6PD deficiency, breast-feeding	Hemolytic anemia

malaria while abroad that included artesunate therapy (5 10-day courses and one 10-day course of chloroquine) for treatment of 3 separate episodes of fever, chills, and malaise. However, he had been fully adherent to his malaria chemoprophylaxis with doxycycline.

His physical examination was significant for tremors, restlessness, hyperreflexia, and spasticity. Laboratory evaluation was normal, as were a chest radiograph and brain MRI. Immunofluorescent antibody testing for detection of antibodies to each human Plasmodium species showed antibody titers < 1:16, consistent with no previous malaria exposure.

COMMENTARY

Fortunately, this patient's symptoms improved markedly after discontinuation of his antimalarial therapy. Fever in travelers to malaria-endemic regions should produce a high index of suspicion for malaria. Each of the 4 human Plasmodium species cause serious febrile illness, and *P. falciparum* is responsible for substantial mortality, primarily for infants and children in holoendemic regions of sub-Saharan Africa. There is a dictum in the field of infectious diseases that "the first 10 diagnostic possibilities for the cause of fever in a traveler are malaria until proven otherwise." In this case, multiple repeat courses of artemisinin derivatives were given to a patient who simply never had malaria!

Treatments given empirically to travelers who become ill when they are abroad can pose a serious threat to any traveler's well being. Trade in pharmaceutical agents is not always regulated, and there could be insufficient or inactive ingredients present in labeled products. Staff with little formal training may be responsible for taking care of patients. Safety and tolerability of the available antimalarials are outlined in *Table 2*, obtained from a recent review of antimalarial medications in the *New England Journal of Medicine*.[2]

The artemesinins are potent compounds derived from the Chinese wormwood plant *Artemesia annua*. They have rapid antiparasitic activity, and can reduce the malaria parasitemia burden 4-fold within each cycle. However, significant neurotoxicity had been documented in rats during early studies of these compounds.[3] Currently, they are used widely in southeast Asia for malaria, given daily for 7 days. They have been combined with other agents as well. Artesunate-clindamycin therapy in 46 Gabonese children with uncomplicated malaria was found to be comparable to quinine-clindamycin in 48 Gabonese children treated for malaria, in the analysis of cure rates, safety, and tolerability.[4] The only neuropsychiatric symptom noted was headache found in small numbers in both groups. *Artesunate-clindamycin* and other artemisinin-based

combinations will likely achieve more use in those regions where the rate of malaria transmission is high. Interest in their approval for use in the United States is increasing. This study by Franco-Paredes and colleagues is an important observation that perhaps delineates some limits of artemisinin compounds and their potential to confer significant neurotoxicity during the management of malaria. ■

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CME Question

8. Which of the following is true regarding Guillain Barré syndrome? Guillain Barré syndrome:

a. occurs commonly after routine vaccinations.
b. can be associated in 95 % of affected patients with a recent *Campylobacter jejuni* infection.
c. is often associated irreversible paralysis.
d. occurred with a slightly increased incidence in recipients of the swine flu vaccine in 1976.
e. now precludes the use of polyvalent meningococcal vaccines.

9. Regarding infectious diseases associated with Hurricane Katrina, which statement is true?

a. Wound infections caused by *Vibrio vulnificus* and *Vibrio parahaemolyticus* occurred as a result of exposure to flood water.
b. Wound-associated Vibrio infection can present as cellulitis, vesicles, and bullae.
c. *V. vulnificus* and *V. parahaemolyticus* can be acquired through eating contaminated shellfish.
d. Persons with underlying liver disease can have severe infection from *V. vulnificus*.
e. All of the above statements are true.

10. Which statement is correct?

a. Various marine fish species that are commonly served in the United States are a major source of fishborne parasites.
b. Various marine fish species that are commonly served overseas are a major source of fishborne parasites.
c. Although various marine fish harbor larvae, fish that are preferentially served in Japanese restaurants are rarely contaminated with Anisakis larvae.

11. The use of artemesinin derivatives for the treatment of falciparum malaria may be limited by:

a. current widespread falciparum resistance in southeast Asia
b. potential neurotoxicity during therapy
c. adverse events during pregnancy
d. cost in the developing world
e. inability to utilize these agents with other antimalarial medications

Answers: 8. (d); 9. (e); 10. (c); 11. (b)

CME Objectives

The objectives of *Travel Medicine Advisor* are:

-To present the latest data regarding the diagnosis and treatment of various travel-related diseases;

-To present new data concerning recommended precautions and prophylaxis for patients traveling to specific areas of the world; and

-To alert the readers to recent disease outbreaks and epidemics. ■

Readers Are Invited

Readers are invited to submit questions or comments on material seen in or relevant to *Travel Medicine Advisor*. Send your questions to: Leslie Hamlin—Reader Questions, *Travel Medicine Advisor*, c/o Thomson American Health Consultants, PO Box 740059, Atlanta, GA 30374. ■

PHARMACOLOGY WATCH

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

Beta-Blockers Therapy for the Treatment of Hypertension

Beta-blockers should not be recommended as first-line therapy for hypertension in patients without heart disease, according to a new study. Researchers from Sweden performed a meta-analysis on 13 randomized controlled trials comparing treatment with beta-blockers with other antihypertensive drugs. Seven other studies were reviewed in which beta-blockers were compared with placebo or no treatment. The relative risk of stroke was 16% higher for patients who were treated with beta-blockers (95% CI, 4-30%) compared to other drugs. Beta-blockers reduced the relative risk of stroke by 19% compared to no treatment or placebo; however, this was about half the reduction expected from previous hypertension trials. There was no difference seen in the rates of myocardial infarction or overall mortality. A possible mechanism for these findings is that beta-blockers reduce brachial blood pressure out of proportion to central blood pressure compared with other antihypertensives.

The authors suggest that beta-blockers are less effective than other antihypertensive drugs in preventing stroke, and should not be a first choice in the treatment of primary hypertension (Lindholm LH, et al. Should Beta Blockers Remain First Choice in the Treatment of Primary Hypertension? A Meta-Analysis. *Lancet*. 2005;366:1545-1553). This same group published a study in 2004, suggesting that atenalol was a poor choice for treatment of hypertension (Carlberg B, et al. Atenolol in Hypertension: Is It Wise?*Lancet*. 2004;364:1684-1689). An accompanying editorial states "Surely, therefore, the era of beta-blockers for hypertension is over," but suggests that these drugs should not be discontinued abruptly, and should be discontinued with extreme caution in patients with coronary artery disease (Beever DG, et al. The End of Beta Blockers for Uncomplicated Hypertension? *Lancet*. 2005;366:1510-1512).

Treatments for Acute Migraine

Two studies in the September issue of the Journal of Headache find that sumatriptan alone is inferior to other treatments for acute migraine. In the first study, 972 migraine patients were randomized to treatment with sumatriptan 50 mg, naproxen sodium 500 mg, sumatriptan 50 mg plus naproxen 500 mg, or placebo at the onset of headache symptoms. The sumatriptan plus naproxen group fared the best, with 46% of subjects achieving a 24-hour pain relief response. Sumatriptan alone resulted in 29% of patients achieving the same result, while naproxen alone resulted in the 25% response, and placebo resulted in a 17% response ($P < .001$). Relief of pain at 2 hours was achieved in 65% of the combination group, 49% of the sumatriptan patients, 46% of naproxen patients, and 27% of placebo patients ($P < .001$). The incidence of recurrent headache 24 hours later was also lowest in the sumatriptan plus naproxen group. Other migraine symptoms, includ-

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ing nausea, photophobia, and phonophobia were also most effectively treated with sumatriptan plus naproxen. Adverse effects were similar in all the treatment groups (Smith TR, et al. Sumatriptan and Naproxen Sodium for the Acute Treatment of Migraine. *Headache*. 2005;45:983-991). In the second study, sumatriptan was compared with acetaminophen-aspirin-caffeine (AAC) in the early treatment of migraine. In a randomized, controlled clinical trial, 171 patients took either sumatriptan 50 mg or AAC (acetaminophen 500 mg, aspirin 500 mg, and caffeine 130 mg [Excedrin Extract Strength 2 tabs], or Excedrin Migraine 2 tabs at the first sign of a migraine attack. AAC was significantly more effective ($P > .05$) than sumatriptan in the early treatment of migraine, as shown by superiority and summed pain intensity difference, pain relief, pain intensity difference, response, sustained response, relief of assisted symptoms, use of rescue medications, disability relief, and global assessments of effectiveness (Goldstein J, et al. Acetaminophen, Aspirin, and Caffeine Versus Sumatriptan Succinate in the Early Treatment of Migraine: Results From the ASSET Trial. *Headache*. 2005;45:973-982).

Statin Therapy for ACS Patients

Early aggressive statin therapy is beneficial for patients with acute coronary syndrome (ACS), according to a new study. In a continuation of the Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis In Myocardial Infarction 22 (PROVE IT -TIMI 22) trial, the timing of intensive statin therapy was evaluated in patients with acute coronary syndrome. A total of 4162 patients with ACS were randomized to intensive statin therapy with atorvastatin 80 mg or standard therapy with pravastatin 40 mg. The composite end points of death, MI, or rehospitalization for recurrent ACS were determined for each group at 30 days. ACS patients who were started in the hospital on intensive statin therapy fared better than those with standard therapy (composite end point at 30 days 3% intensive therapy vs 4.2% standard therapy [HR = 0 .72; 95% CI, 0.52 to 0.99; $P = .046$]). The authors conclude that ACS patients should be started on aggressive statin therapy in the hospital and continued long-term (Ray KK, et al. Early and Late Benefits of High-Dose Atorvastatin in Patients With Acute Coronary Syndromes: Results from the PROVE IT-TIMI 22 Trial. *J Am Coll Cardiol*. 2005;46:1405-1410). In another follow-up from the PROVE IT-TIMI 22 study in the same Journal, researchers looked at whether very low LDL levels from aggressive statin therapy are associated with adverse effects. Thirty-one percent of patients treated with atorvastatin achieved LDL levels between 80 and 60mg/dL, with another 34% between 60 and 40 mg/dL, and 11% less than 40 mg/dL. There were no significant differences in safety parameters, including muscle, liver, or retinal abnormalities, intracranial hemorrhage, or death in the very low LDL groups. Patients with LDL levels less than 60 had fewer major cardiac events, including death MI and stroke. The authors conclude that very low LDL levels are not associated with adverse effects, and appear to be associated with fewer adverse cardiovascular outcomes (Wiviott SD, et al. Can Low-Density Lipoprotein Be Too Low? The Safety and Efficacy of Achieving Very Low Low-Density Lipoprotein With Intensive Statin Therapy: A PROVE IT-TIMI 22 Substudy. *J Am Coll Cardiol*. 2005;46:1411-1416).

The Correct Dosing for Onychomycosis

Many physicians have prescribed terbinafine in a pulse-dosing regimen of 2 pills per day for one week, one week a month, for 3 to 4 months for the treatment of onychomycosis. The regimen is thought to increase compliance, as well as reduce cost. Pulse dosing however is not an approved therapy, and now a new study suggests that it is not as effective as once daily dosing.

The study recruited 306 volunteers with onychomycosis, involving at least 25% of the toenail. Patients were randomized to terbinafine 250 mg daily for 3 months or terbinafine 500 mg daily for one week per month for 3 months. Mycological cures were higher with once-a-day dosing (71% vs 58.7%; $P = .03$). Clinical cures were also higher with once-a-day dosing (44.6% vs 29.4%; $P = .007$), as were complete cures of target toenail (40.5% vs 28.0%; $P = .02$), and complete cure of all 10 toenails (25.2% vs 14.7%; $P = .03$). Tolerability of the regimens did not differ significantly between groups.

The authors conclude that once daily dosing appears to be superior to pulse dosing, however, they also found "this expensive therapy to me much less effective than previously believed, particular for achieving complete cure of all 10 toenails" (Warshaw EM, et al. Pulse Versus Continuous Terbinafine for Onychomycosis: A Randomized, Double-Blind, Controlled Trial. *J Am Acad Dermatol*. 2005;53:578-584).

FDA Actions

The FDA has approved the once-a-day oral iron chelator for the treatment of chronic iron overload due to blood transfusions. Novartis will market deferasirox (Exjade) as an oral alternative to intravenous chelating agents. ■