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Disabilities Among Foreign-Born Adoptees

ABSTRACT & COMMENTARY

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Ms. Keating and Dr. Fischer report no financial relationships relevant to this field of study.

Synopsis: *At an approximate rate of 12%, disabilities are twice as common among internationally adopted children in the United States compared to the general U.S. population, but the rates of disability are similar between foreign-born and U.S.-born adopted children. Children adopted from China and Korea have much lower risks of disability than do children from eastern Europe.*

Source: Kreider RM, Cohen PN. Disability among internationally adopted children in the United States. *Pediatrics* 2009;124:1311-1318.

Kreider and Cohen studied more than 13,000 internationally adopted children ages 5 to 15 and more than 155,000 domestically adopted children ages 5 to 15; they then extrapolated findings from this sample to the entire U.S. population. (*Data are summarized in Table.*) Data were collected from the 2000 U.S. Census. Disability rates for internationally adopted children in the United States were estimated by country of origin, adjusting for age at adoption, gender, current age, and parental characteristics. These rates were compared to the disability rates for children adopted domestically. Disabilities identified are sensory (severe vision or hearing impairment), physical (limitation in walking, climbing stairs, reaching, lifting, or carrying), mental (learning, remembering, or concentrating), and self-care (dressing, bathing, or getting around inside the home).

It was correctly predicted that adopted children had higher rates of disability than non-adopted children. Internationally adopted children have disability rates (11.7%) similar to those children adopted domestically (12.2%) and more than twice the rate for non-adopted children in that age range (5.8%). Disability rates among children adopted from China and Korea had lower adjusted disability rates than domestically adopted children, while children adopted from Russia, Romania, and Bulgaria all had higher odds of disability than did domestically adopted U.S. children. Children who were adopted as infants had the lowest disability rates relative to those adopted at ages 2 to 9. Adoptive parents' education showed no significant effect in the international adoption models. Children who were adopted by non-Hispanic white parents had higher adjusted odds of disability.

Table. Disability Status of Adopted Children Aged 5 to 15: 2000 U.S. Census

Adoption status	n	% with at least 1 disability
U.S. Native Adopted Children	972,200	12.2
Internationally Adopted Children	82,220	11.7
Place of birth (10 selected)		
Korea	29,735	7.1
Russia	8,070	17.4
China	4,285	3.7
Colombia	4,205	12.7
Romania	4,010	21.2
India	3,730	16.2
Guatemala	3,055	11.3
Paraguay	2,310	12.5
Mexico	1,995	15.6
Bulgaria	7,00	21.9

■ COMMENTARY

Professionals practicing travel medicine often see adopting families for either pre-travel or post-immigration consultation. It behooves them, even as it behooves other child health and education professionals as well as adoptive and prospective adoptive parents, to be aware of the risk for disabilities among internationally adopted children.

Overall, there was no difference in the rate of reported disabilities between domestically and internationally adopted children aged 5 to 15, although both had rates that were more than twice as high as the general population of children. A number of factors potentially could explain the higher rates of disability among adopted children. First, the health statuses and behaviors of birth parents before or during pregnancy may contribute to a child's higher risk for early health problems and disabilities. A second factor that may contribute is deprivation during the institutional care within orphanages, and longer exposure to these conditions may lead to long-term disabilities. Third, the intentional selection of children with disabilities for placement and acceptance during international adoption, either because domestic families do not choose to raise children already identified as disabled or because some U.S. parents seek disabled adoptions for altruistic reasons, may be a factor that explains the higher rate of disability.

Several studies of internationally adopted children have identified physical, psychosocial, and academic challenges among foreign-born adoptees. One recent study has shown that although international adoptees can adequately catch up to their non-adopted peers in certain areas of development, they often experience difficulties with attention regulation, executive function, and sensory processing. These deficits may increase the risks for later school problems.[1] Attention deficit disorders are more common in international adoptees than in native-born Swedes.[2] Furthermore, children adopted internationally from institutions have been shown to have even more problems. A recent study showed that 44% of post-institutionalized children had stunted

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growth and were more likely to fall behind academically in school; adverse outcomes relate to the duration of institutionalization but not to the country of origin.[3] Another study showed that post-institutionalized children frequently demonstrate persistent socio-emotional difficulties, such as an unusual lack of social reserve with unfamiliar adults.[4]

In addition to mental and behavioral effects, institutionalization also has physiological and biological effects. A study of post-institutionalized children showed that early social deprivation in an institution may contribute to long-term regulatory problems of the stress-responsive system.[5] Furthermore, it has been shown that institutionalization impairs regulation of the hypothalamic-pituitary-adrenocortical (HPA) axis, potentially increasing vulnerability to stressors throughout life.[6]

Thus, the risk of identified disability in foreign-born adoptees varies with the country of origin but is similar to the risk of disability in U.S.-born adoptees. Children adopted from institutional settings carry additional risks of social and academic challenges. There are other risks related to international adoption that impact the practice of travel medicine. Hepatitis A has been identified in international adoptees and, subsequently, their direct and indirect contacts.[7] Hepatitis A vaccination now is recommended for household members and other close personal contacts of adopted children newly arriving from countries with high or intermediate hepatitis A endemicity.[8] Helpful literature to guide physicians caring for international adoptees and their families has recently been reviewed.[9] ■

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Land-to-sea Transmission of Toxoplasmosis ... And Back Again

ASTM CONFERENCE COVERAGE

By Mary-Louise Scully, MD

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At the recent 58th Annual Meeting of American Society of Tropical Medicine and Hygiene held in Washington D.C., Dr. Patricia Conrad of the University of California–Davis School of Veterinary Medicine provided an excellent presentation during the Scientific Session on Protozoa entitled "Tracking *Toxoplasma gondii* from Land to Sea." Conrad and her colleagues have been exploring the complex relationship between marine and terrestrial environments in toxoplasmosis transmission to California sea otters. Their research shows that the increasing prevalence of toxoplasmosis in California sea otters is linked to coastal fresh water runoff of infective *Toxoplasma gondii* (*T. gondii*) oocysts from cat feces, both domestic and feral. These findings are especially noteworthy in that a recent study found ingestion of raw or undercooked clams, oysters, and mussels to be an emerging risk factor for human toxoplasmosis acquisition as well.[1]

Sea otters were once abundant along the Pacific Rim, but these animals were hunted to near extinction for their soft, dense, highly valued fur, often referred to as "soft gold" among hunters. In 1911, sea otter hunting was finally banned under an international treaty signed by

Russia, Japan, Great Britain, and the United States. Under legal protection, some sea otter populations in Alaska and the Pacific Northwest have rebounded. However, the California southern sea otter (*Enhydra lutris nereis*) has struggled and remains listed as a threatened species numbering only about 2,800. The causes for their decline are likely multi-factorial, but a partial explanation is parasitic infections such as *T. gondii* and *Sarcocystis neurona*.

T. gondii can infect a wide variety of animals, but domestic and wild felids (felines) are the only definitive hosts where sexual multiplication of the parasite results in formation of oocysts that are passed in the feces, sporulate in the environment, and are infective to susceptible hosts. Cats are infected by eating tissue cysts of infected birds or rodents or by eating sporulated cysts from other cats. Under laboratory conditions, cats can shed as many as 500 million oocysts, and they may shed oocysts for up to 20 days. The natural instinct of cats to bury their feces and defecate in shaded areas can allow the cysts to remain infective for as long as 18 months.[2] These infective oocysts in soil may then be transported into freshwater and marine waters via sewage, storm, and freshwater runoff.

It is known that *T. gondii* can cause fatal encephalitis in California sea otters. Conrad and colleagues studied 223 live and dead sea otters between 1997 and 2001 and found a seroprevalence rate of 42% (49/116) for live otters and 62% (66/107) for dead otters. Importantly, they found that otters sampled near coastal areas of freshwater runoff were approximately three times more likely to be seropositive for *T. gondii* compared to otters living in areas of low-flow runoff.[3] Therefore, land-based surface runoff appears to be the mechanism by which infective *T. gondii* oocysts enter the marine environment.

The exact means by which sea otters and other marine mammals acquire *T. gondii* in the marine environment is unknown. Previous laboratory studies demonstrated that *T. gondii* oocysts may be concentrated by filter feeding marine bivalves such as mussels, but more recent research has shown that specific feeding preferences of sea otters also may affect toxoplasmosis prevalence. Sea otters with diets composed of $\geq$ 10% marine snails were 12 times more likely to be infected with *T. gondii* than sea otters that ate fewer marine snails. In contrast, sea otters with diets consisting mainly of abalone had a much lower risk of infection.[4] In another study, the specific physical properties of *T. gondii* oocysts (i.e., the loss of electrical charge in saline waters) was shown to promote flocculation and sedimentation of *T. gondii* oocysts in areas where marine and fresh waters meet, such as estuaries and near-coast habitats. These are areas where marine snails and sea otters frequently feed, but also where humans may be more exposed by water-related activities to infective oocysts as well.[5]

Several human toxoplasmosis outbreaks have been epidemiologically linked to contaminated water sources, including one outbreak in a municipal water reservoir in British Columbia, Canada.[6] It is also known that wastewater treatment practices and chlorination are not effective at destroying the oocysts of *T. gondii* and they can remain viable in seawater for up to 6 months. The Palo Alto Medical Foundation Toxoplasma Serology Laboratory in conjunction with the CDC recently published a case control study of 148 adults infected with *T. gondii*. In this study, eating raw oysters, clams, or mussels was a risk factor for acquisition of toxoplasmosis in the subset of patients asked this question. Other risk factors were eating raw ground beef or rare lamb, working with meat, eating locally produced cured, dried, or smoked meat, drinking unpasteurized goat's milk, and having three or more kittens.[1]

It is estimated that 32% of households in the United States own cats (an estimated 78 million cats); an additional 73 million cats are feral.[7] With these large numbers, the potential land-to-sea transport of infectious *T. gondii* oocysts is impressive. Cat owners can help by not flushing cat litter down the toilet. Instead, cat litter should be bagged and disposed of in approved landfills where runoff is well controlled. This includes cat litter products that are advertised as "flushable litter." Some cat litter products may even be advertised as "eco-friendly" to be added to compost piles, but this should be avoided as well. In 2006 California Governor Arnold Schwarzenegger signed a bill into law requiring that all cat litter sold in California carry a warning label not to dispose of the litter in toilets or storm drains. However, many people remain unaware or perhaps unconvinced of the importance of this law.

What is in our backyards, be it cat feces or the chemicals used in our homes or lawns, invariably will end up in our oceans. The connection between the health of marine mammals and human health is more evident each day. Scientists in both realms now realize that the environment we share together means we share the same risks and, eventually, the same fates. As Jean-Michel Cousteau, the renowned explorer and passionate advocate of protection of the marine environment, tells us, "Protect the oceans, and we protect ourselves."

More information about marine conservation and sea otter research can be found at www.oceanfutures.org and www.seaottersresearch.org. ■

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Incidence of Yellow Fever Vaccine-Associated Neurotropic Disease: Meningitis and Meningoencephalitis in Adults Within 30 Days of Vaccine Administration

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Synopsis: *A retrospective analysis was performed of all serious neurologic events that resulted in hospitalization within 30 days of yellow fever vaccination between 2000-2008.*

Source: Guimard T, Minjolle S, Polard E, et al. Short report: Incidence of yellow fever vaccine-associated neurotropic disease. *Am J Trop Med Hyg* 2009;81:1141-1143.

FOUR ADULTS WITH EITHER PROBABLE OR DEFINITE yellow fever (YF) vaccine-associated meningitis or meningoencephalitis were hospitalized, yielding an incidence of 9.9/100,000 vaccine doses (95% CI = 2.7-25.4/100,000). This is 10 times higher than previous estimates that did not include acute meningitis as a defining neurologic event. All patients were first-time YF vaccine recipients, and symptoms resolved in all but one, for whom cerebellar syndrome and attention deficit disorder persisted. The male-to-female ratio was 3:1, and ages ranged from 21 to 55 years.

■ COMMENTARY

There are three kinds of fatal adverse events caused by YF vaccine: anaphylaxis, YF vaccine -associated viscerotropic disease (YF-AVD), and YF vaccine-associated neurotropic disease (YF-AND). YF-AVD occurs in approximately 0.3-0.4 of 100,000 vaccinations, and risk factors identified to date include advanced age and history of thymus disease.[1] YF-AND classically has included encephalitis, acute disseminated encephalomyelitis, and Guillain-Barré syndrome. Criteria for association with the YF vaccine when these conditions have occurred include the presence of IgM antibodies against YF in cerebrospinal fluid (CSF) or isolation of the virus from the blood or CSF. (*See Table.*) The incidence of YF-AND was 0.4-0.8 per 100,000 vaccinations when evaluated through a passive reporting system.[1] However, active surveillance during mass vaccine campaigns in Brazil identified 12 cases of acute lymphocytic meningitis diagnosed within 30 days of vaccine administration, suggesting an incidence of 3.9/100,000 doses.[2]

This report of four cases of adult neurotropic disease comes from an institution that administered 40,404 vaccine doses over an eight-year period. Only severe neurologic events were captured by this retrospective study of hospitalized patients, which could have resulted in an underestimate of the number of neurologic complications of YF vaccine. Delay between YF vaccination and symptoms warranting admission ranged between 19 and 23 days, which is consistent with a previous report of 15 cases of YF-AND from the Yellow Fever Safety Working Group.[3] In the current study, only one case had YF-IgM antibody documented in his CSF, and this 41-year-old had a history of testicular cancer, possibly marking him as an immunocompromised host. The other three probable cases (*see Table*) did not have enough

Table. Criteria on Relationship of Yellow Fever Vaccine to Defining Neurologic Conditions*

Encephalitis		
	Suspect	• Onset of symptoms 1-30 days after vaccination with yellow fever vaccine (YEL), either given alone or in combination with other vaccinations *AND* • No evidence of other diagnoses causing disease
	Probable	Suspect encephalitis *AND* one or more of the following: • Vaccine-type yellow fever virus isolated from the blood (> 7 days post-vaccination) • Yellow fever 17D virus concentration in serum on any day exceeds 1,000 pfu/mL
	Definite	Suspect encephalitis *AND* one or more of the following signs: • Yellow fever-specific IgM antibody detected in CSF • Yellow fever 17D virus isolation from CSF • Molecular amplification of vaccine-type virus from CSF
Acute Disseminated Encephalomyelitis (ADEM)		
	Suspect	• Onset of symptoms 1-30 days after vaccination with yellow fever vaccine (YEL), either given alone or in combination with other vaccinations *AND* • No evidence of other diagnoses causing disease
	Probable	Suspect ADEM *AND* • Yellow fever vaccine given alone
Guillain-Barré Syndrome (GBS)		
	Suspect	• Onset of symptoms occurs 1-30 days after vaccination with yellow fever vaccine (YEL), either given alone or in combination with other vaccinations *AND* • No evidence of other diagnoses causing disease
	Probable	Suspect GBS *AND* • Yellow fever vaccine given alone

* Adapted from McMahon A, Eidex R, Marfin A, et al. Neurologic disease associated with 17D-204 yellow fever vaccination: A report of 15 cases. *Vaccine* 2007;25:1727-1734.

CSF preserved to check CSF IgM levels. Cerebrospinal fluid examination in the four cases showed pleocytosis (10-82 cells/mm^3) with 64-84% lymphocytes and slightly elevated protein levels (0.4-0.68 g/L).

The YF vaccine studied in this institution was the 17D-204 strain (StamarilR, Aventis Pasteur, Marcy L'Etoile, France) similar to YF-VaxR, the commercially available YF vaccine manufactured by Sanofi Pasteur in the United States. Of interest, all four patients with neurologic disease in the current study had received YF vaccine for the first time; patients who have developed YF-AVD to date have also been primary vaccinees. A limitation of the study was reliance on retrospective data, which included only adverse events severe enough to warrant hospitalization. Nevertheless, this report highlights the need for careful evaluation of the need for YF vaccination prior to travel. The average risk of developing YF for a non-immunized traveler during a one-month trip to endemic areas of South America and Sub-Saharan Africa is between 10 and 100 per 100,000 travelers, and this study's incidence of neurologic events was 9.9/100,000. Fortunately, three of the four vaccine recipients who developed neurologic disease in this study experienced apparently complete recovery. Limited data are available regarding whether 17D live attenuated viruses cause residual neurologic sequelae after YF-AND. Wild-type YF virus infrequently causes encephalitis or other neurologic disease. YF vaccine-associated neurotropism causing encephalitis was first described in infants receiving the 17D-based vaccines. Fortunately, since limiting administration to persons older than 6 months of age in 1969, there have been only two neurologic fatalities: a previously healthy 3-year-old, in whose brain a mutant variant of the vaccine was isolated, and a 53-year-old man with HIV infection who died from encephalitis nine days following the vaccination.[2]

In conclusion, although the risk of neurologic disease after YF-vaccine is still small, it may be higher than previously recognized, and the decision to administer the vaccine to persons at risk should take into consideration epidemic YF activity, duration of travel, and the likelihood of exposure to vector mosquitoes. Clinicians who observe any neurologic symptoms within 30 days of YF vaccination, especially after primary vaccination, should report to the Vaccine Adverse Event Reporting System at http://vaers.hhs.gov/index. Aseptic meningitis should now be considered a defining neurologic adverse event caused by YF vaccination, along with acute disseminated encephalomyelitis, Guillain-Barré syndrome, and encephalitis. ■

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Bacterial Co-infection in H1N1 Influenza

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This article originally appeared in the December 2009 issue of Infectious Disease Alert.

Source: Bacterial coinfections in lung tissue specimens from fatal cases of 2009 pandemic influenza A (H1N1) — US, May-August 2009. *MMWR.* 2009;58.

DATA EARLY ON IN THE PANDEMIC INFLUENZA OUTBREAK suggested that most severely ill patients with Influenza A were not suffering from bacterial co-infection. An initial *MMWR* report found no evidence of bacterial superinfection in 30 patients hospitalized in April-May 2009 with confirmed H1N1 in California,[1] although 15 of 25 (60%) with chest radiographs had pulmonary infiltrates. Two-thirds had multilobar infiltrates, and four patients required mechanical ventilation. A second report in the *MMWR* this summer described an additional 10 patients with H1N1 influenza requiring critical care in Michigan lacking evidence of bacterial pneumonia.[2]

These reports may have been misleading, insomuch as causative agents of pneumonia are difficult to identify, even under optimal circumstances. Newer data, based on autopsy specimens, suggest that nearly one-third of patients with fatal H1N1 illness have evidence of super-infecting bacterial pneumonia. Respiratory specimens (lung, trachea, and large-airway specimens) collected at autopsy from 77 patients with laboratory-confirmed fatal H1N1 infection were evaluated for evidence of bacterial infection. This included tissues stains, immunohistochemical antibody testing for various bacterial pathogens (including antibodies to *S. pneumoniae*, *S. pyogenes*, *S. aureus*, *H. influenza* but not Legionella spp.), and PCR-based assays to further characterize streptococcal and pneumococcal infection. H1N1 infection was confirmed in 41 of the patients before death and identified in 36 patients post-mortem.

Of the 77 fatal cases of H1N1 infection submitted for analysis, 22 (29%) had histopathological, immunohistochemical, and molecular evidence of bacterial pneumonia.

Streptococcus pneumoniae was the most frequently identified pathogen, occurring in 10 persons (13%), followed by *S. aureus* (9.1%), *S. pyogenes* (7.8%), *S. mitis* (2.6%), and *H. influenza* (1.3%). Multiple bacterial pathogens were found in four patients (5%). The mean age at death was 31 (range, two months to 56 years), and half were male. The median duration of illness, available for 17 of the patients, was six days (range, 1 to 25 days). Fourteen had received some kind of medical care, at least seven had received antibiotics, and eight had been hospitalized. In 21 patients for whom this kind of information was available, 16 had significant underlying medical conditions known to increase the risk for severe influenza infection (five were described as obese, two each with diabetes, asthma, and Down syndrome, and one with HIV infection).

The presence of bacterial pneumonia in nearly one-third of patients with fatal H1N1 infection should be viewed as a minimum estimate of the risk of bacterial super-infection in such patients. Even with the best techniques, super-infecting bacterial pneumonia in patients with viral pneumonia or ARDS may be difficult to confirm. Based on this data, empiric antibacterial therapy should be considered for critically ill patients with influenza, at least until their respiratory status has stabilized or improved. An agent with activity against MRSA should be considered, especially in persons at risk. ■

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CME Questions

1. Which of the following statements regarding disability and adoption is *not* true?
   a. International adoptees from China and Korea are less likely to have disabilities than U.S.-born adoptees.
   b. The duration of institutionalization prior to adoption is linked to the risk of academic difficulties.
   c. Hepatitis A vaccination is recommended for childcare workers caring for international adoptees.
   d. Adoptees from Eastern Europe are at less risk of disability than are adoptees from Korea.

2. All of the following statements regarding the biology of *Toxoplama gondii* are true *except*:
   a. The organism can cause clinical illness in humans and sea otters
   b. Oocysts of *T. gondii* can remain infective in soil for more than 12 months.
   c. *Toxoplasma gondii* requires felines as definitive hosts.
   d. Oocysts of *T. gondi*i are killed by chlorination.
   e. *T. gondii* has been associated with waterborne human outbreaks.

3. Aseptic meningitis can be considered associated with the yellow fever vaccine if meningitis:
   a. occurs within 30 days of administration of YF vaccine and if CSF IgM antibodies to YF are positive, even though YF virus is not isolated in blood or CSF
   b. occurs within two days of administration of YF vaccine even if the virus is not isolated from the blood or CSF and enterovirus virus is isolated from CSF
   c. occurs in an HIV-positive patient who received YF vaccine two years prior to the aseptic meningitis presentation, as YF virus can remain latent in HIV positive patients

CME Objectives

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.

Answers: 1. d; 2. d; 3. a

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*.

Dabigatran: An Oral Direct Thrombin Inhibitor

In this issue: Results from a Phase 3 study of dabigatran, intensive lipid-lowering in CVD, H1N1 vaccine dosing and efficacy, and FDA Actions.

Anticoagulation without monitoring?

Dabigatran is an oral direct thrombin inhibitor, currently being used in many countries as an alternative to warfarin. It is anxiously awaited in this country primarily because, unlike warfarin, it does not require monitoring with blood tests. The drug has been shown to be as effective as warfarin in preventing stroke in patients with atrial fibrillation (*N Engl J Med* 2009;361:1139-1151).

A new study published in December 2009 compares the two drugs in the treatment of acute venous thromboembolism. In a randomized, double-blind, non-inferiority trial, patients with acute venous thrombus embolism were given a median of 9 days of parenteral anticoagulation therapy, then were randomized to oral dabigatran (150 mg twice a day) or warfarin that was dose-adjusted to achieve an INR of 2.0-3.0. The primary outcome was 6-month incidence of recurrent symptomatic, objectively confirmed venous thromboembolism and related deaths. Of the patients randomized to receive dabigatran, 2.4% had recurrent venous thromboembolism compared to 2.1% of patients on warfarin (difference in risk of 0.4%; 95% confidence interval [CI], -0.8 to 1.5; $P < 0.001$ for the prespecified non-inferiority margin). Major bleeding episodes occurred in 1.6% of patients on dabigatran vs 1.9% of patients on warfarin. Episodes of any bleeding were 16.1% with dabigatran and 21.9% with warfarin. There was no difference in the number of deaths, acute coronary syndromes, or abnormal liver function tests between the two groups. Treatment was discontinued due to adverse events in 9% of patients on dabigatran and 6.8% of patients on warfarin. The authors concluded that for treatment of acute venous thromboembolism, a fixed dose of dabigatran is as effective as warfarin, has similar safety, but does not require laboratory monitoring (*N Engl J Med* 2009;361:2342-2352).

Physicians and patients alike in the United States have been awaiting an orally effective anticoagulant that doesn't require monitoring. Dabigatran, a direct thrombin inhibitor, may soon fill that role. The drug, which has the additional advantage of having minimal drug and food interactions, has been available in Canada and Europe for almost 2 years, and with the completion of Phase 3 trials such as this one, there is speculation the FDA may take action this year. ■

Intensive lipid-lowering and CVD

Follow-up analysis of two of the most famous lipid-lowering trials confirms that intensive lipid-lowering therapy continues to be beneficial in the longer term. The PROVE IT-TIMI 22 (Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22) trial, first published in 2004,

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compared moderate lipid-lowering using standard-dose pravastatin to intensive lipid-lowering with high-dose atorvastatin after acute coronary syndrome. The study showed high-dose therapy significantly reduced the occurrence of death, myocardial infarction, stroke, and unstable angina requiring hospitalization or revascularization occurring more than 30 days after the event. The new post-hoc analysis (*J Am Coll Cardiol* 2009; 54:2358-2362) followed patients for up to 2 years and showed continued benefit in reduction of the primary endpoint (16%; P = 0 .005) with high-dose therapy, as well as reduction of additional events (19%; P = 0.009).

The IDEAL (Incremental Decrease in End Points Through Aggressive Lipid Lowering) study compared high-dose atorvastatin with usual dose simvastatin for the prevention of events subsequent to a first event. The study was published in 2005, and while not showing reduction in mortality in the 4.8 years of study, it did show a reduction in secondary cardiovascular outcomes with high-dose therapy. The new analysis looked at not only time to first event, but also second, third, fourth, and fifth events. High-dose therapy significantly reduced subsequent events by 17%-28%. The authors concluded that continued intensive statin therapy continues to be more effective than standard statin therapy, even beyond the first vascular event (*J Am Coll Cardiol* 2009;54:2353-2357).

Both these studies suggest that staying the course with intensive lipid-lowering in patients with cardiovascular disease is an effective long-term strategy. ■

H1N1 dosing and efficacy

Three recent studies in the Dec. 17, 2009, *New England Journal of Medicine* confirm that a single dose of the H1N1 vaccine is effective for most healthy adults and children age 3 and older. In the first study, 240 patients were equally divided to receive 15 µg or 30 µg of hemagglutinin antigen by IM injection. By day 21, antibody titers of 1:40 were observed in 95.0% of patients who received the 15 µg dose and 89.1% of patients who received the 30 µg dose (*N Engl J Med* 2009;361:2405-2413).

In the second study from China, antibody titers were done at 21 days after a first injection of 15 µg with or without adjuvant. A titer of 1:40 was achieved in 75% of subjects between age 3 and 11, 97.1% of subjects between age 12 and 17, 97.1% of subjects between age 18 and 60, and 79.1% of subjects age 61 and older. Alum adjuvant did not significantly raise antibody titers. Although a second injection at 21 days raised antibody titers, the authors conclude that a single dose of 15 µg induced a typically protective antibody response in the majority of subjects between age 12 and 60 (*N Engl J Med* 2009;361:2414-2423).

In the third study, standard H1N1 vaccine was compared to a MF59-adjuvanted vaccine (derived from cell culture rather than egg-based). A number of injection schedules were tested. Local reactions and muscle aches were more frequent in the MF59-adjuvanted vaccine. Although higher antibody titers were seen with the adjuvanted vaccine, significant titers were also seen within non-adjuvanted vaccine within 2-3 weeks (*N Engl J Med* 2009;361:2424-2435).

These findings confirm data previously published in the *Lancet* in the fall of 2009 confirming that one dose of the H1N1 vaccine seems adequate, although two doses may be required for younger children. Currently, the Centers for Disease Control and Prevention (CDC) recommends two doses for children younger than age 10, but the recommendations may change based on these findings.

In related news, the CDC is reporting that safety data regarding the H1N1 vaccine is "reassuring," with a rate of serious complications such as Guillain-Barré syndrome no higher than "background rates." The rate of adverse event reporting has been higher with the H1N1 vaccine compared to seasonal flu; however, most of these reports have been for mild reactions and may be attributed to the higher rate of awareness associated with the new vaccine. ■

FDA Actions

The FDA has approved the first generic version of donepezil (Aricept®) for the treatment of Alzheimer's disease. The new generic will be marketed as 5 mg and 10 mg orally disintegrating tablets, which dissolve on the tongue and do not need to be swallowed. Generic donepezil is expected to be available later this year. ■

An FDA advisory panel is recommending expansion of the indication for rosuvastatin (Crestor®) to include patients with normal cholesterol levels and no history of cardiovascular disease. The recommendation is based on the JUPITER trial, which showed a reduction in cardiovascular risk in patients with normal LDL cholesterol but high C-reactive protein who were treated with rosuvastatin. ■