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Novel Swine-Origin Influenza A H1N1 Virus and Air Travel

ABSTRACT & COMMENTARY

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

Synopsis: *CDC guidance for prevention of novel swine-origin influenza A (H1N1) during air travel focuses on basic measures of hygiene, cough etiquette, and identification and isolation of ill travelers, rather than imposing broad travel restrictions.*

Source: CDC. Interim Guidance for Airlines Regarding Flight Crews Arriving from Domestic and International Areas Affected by Novel H1N1 Influenza. www.cdc.gov/h1n1flu/guidance/air-crew-dom-intl.htm Accessed 5/09/09. CDC. Interim Guidance to Assist Airline Flight Deck and Cabin Crew in Identifying Passengers Who May Have Novel H1N1 Flu. www.cdc.gov/h1n1flu/aircrew.htm. Accessed 5/09/09.

A NOVEL SWINE-ORIGIN INFLUENZA A (H1N1) VIRUS (S-OIV) HAS BEEN identified as the cause of the recent outbreaks of febrile respiratory infection in Mexico with subsequent global spread to more than 28 countries. News of the outbreak quickly triggered the World Health Organization (WHO) and governmental agencies to initiate pandemic preparedness measures that had been developed for the possibility of pandemic avian influenza A (H5N1).

Novel Influenza A (H1N1) is transmitted from person to person in the same ways as seasonal influenza, with droplet exposure from coughing and sneezing of infected people as a primary mode of transmission. In addition, influenza also can be spread through contact with contaminated hands or surfaces and, less often, by airborne (droplet nuclei) routes.

The CDC interim guidelines address concerns about the potential for transmission of novel influenza A (H1N1) during air travel. First and foremost, the absolute importance of ill or potentially infected persons to avoid travel is stressed. Any ill person is advised to stay home from work or school and limit contact with other persons. Next, standard infection control and industrial hygiene practices are stressed, such as frequent hand washing and cough etiquette. Airline flight crews are advised to wear impermeable, disposable gloves on board the aircraft if they need to have direct contact with potentially contaminated surfaces such as airplane seats, tray tables, and lavatories used

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by ill passengers. If a crew member needs to assist an ill person, a facemask at a minimum, but ideally use of a respirator rated N-95 or higher, should be used.

Cabin and flight deck crew should be fully knowledgeable about the possible symptoms of influenza so as to be able to better identify potentially ill travelers. During a flight, if a person shows observable signs of novel influenza A (H1N1) illness, an attempt should be made to isolate the ill person (6 feet) from others, and the ill person should wear a facemask. If a facemask cannot be tolerated, then tissues should be provided with a bag for proper disposal of contaminated items.

If a flight is bound for the United States and a person shows observable signs of an S-OIV illness, the captain is required by law to report the illness to CDC Quarantine Station in the jurisdiction of the airport where the plane is expected to land. The quarantine officials will then make arrangements for appropriate medical assistance, disease control and containment measures, passenger and crew notification and surveillance activities, as well as airline disinfection procedures. Of note, the flight deck crew should ensure that the aircraft air conditioning and ventilation system stay on until all passengers and crew have disembarked to maximize removal of virus particles from the cabin air.

■ COMMENTARY

It is estimated that more than 1 billion people undertake air travel each year. The confined cabin space, prolonged exposure time, and the process of ventilation and recirculation of cabin air raise concerns of increased transmission of respiratory pathogens. Yet it is very difficult to measure the actual rate of transmission of respiratory infections from air travel, in part secondary to the sheer numbers of travelers and the difficulty in proving the source, variable incubation periods of respiratory pathogens, pursuing follow up, and even differentiating cabin exposure from contact within the airline terminal before the flight.[1]

Despite these challenges, several studies have evaluated in-flight transmission of influenza. One well-known example is the 1979 Alaskan passenger jet that suffered engine failure during take-off, which resulted in a 3-hour ground delay. All 54 passengers remained on board during the delay. The index patient developed influenza-like symptoms while on board, and within 72 hours, 40% of the crew and 72% of the passengers became ill with influenza.[2] It was noted that during the 3-hour delay the cabin ventilation was turned off. Mostly as a result of this outbreak, it is now recommended that airplanes with more than 30-minute ground delays keep the aircraft ventilation system in operation.

In a more recent report, a person ill with influenza-like symptoms flew on a 75-seat plane for a 3.5-hour flight. Despite adequate air circulation and filtration, 20 other passengers developed similar illnesses during the next 3-4 days after the flight. All but two of the 20 cases were seated in close proximity to the index patient, supporting the notion that transmission occurred through droplet exposure as the person was coughing and sneezing throughout the flight.[3]

Most commercial passenger airplanes have complex systems to pressurize the air in the cabin, control ventilation and filtering of cabin air, as well as adjust the

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temperature and humidity of the air for the comfort of the passengers. Typically, outside air is compressed, heated, conditioned, and then mixed with an equal (50:50) amount of filtered recirculated air. The recirculation system takes air from the cabin and passes it through high-efficiency particulate air (HEPA)-type filters. These filters remove particles and microorganisms sized as small as 0.3 μ. This should be efficient for removal of most bacteria, which are approximately 1.0 μ in size. Viruses, although often much smaller in size (0.01-0.10 μ), are thought to form clumps or ride on dust particles that are large enough to become trapped in the HEPA filter as well.[4]

In the ventilation systems of most modern aircraft, air circulation is laminar, i.e. side to side, where air enters the cabin at the overhead system of a seat row and leaves the cabin at the floor level of the same row. This should result in very little air exchange front to back within the cabin, but rather mostly along the seat row. The importance of physical proximity to an index case was demonstrated during the SARS outbreak in which people seated in the three rows in front of the index patient had a higher relative risk of developing illness.[5] Droplet exposure through coughing and sneezing of the ill passenger would be consistent with this proximity. The CDC interim guidance for in-flight measures that recommend physical isolation and masking of ill passengers puts this concept into action.

The use of U.S. quarantine centers addressed in the CDC interim guidance has an interesting history. The first U.S. quarantine station and hospital were built in 1799 at the port of Philadelphia in response to the 1793 yellow fever outbreak. In 1878, the National Quarantine Act moved the quarantine powers from the states to the federal government. In 1967, the CDC (then known as the National Communicable Disease Center) took over federal quarantine functions. During the 1970s, the number of quarantine stations was reduced from 55 to 8, but after the September 11, 2001, attack on the World Trade Center and later with the 2003 SARS outbreak, the CDC increased the number of quarantine centers from 8 to 20. The quarantinable diseases include cholera, diphtheria, infectious tuberculosis, plague, smallpox, yellow fever, viral hemorrhagic fevers, and SARS (added in April 2003). New types of influenza with pandemic potential were added in 2005.

Some experts feel that the recent novel influenza A (H1N1) outbreak serves as a good testing ground for the pandemic preparedness policies adopted for avian influenza A (H5N1) and the new strengthened International Health Regulations. In an address to world health administrators on May 9, 2009, WHO Director-General Dr. Margaret Chan stated, "The world is better prepared for an influenza pandemic than at any time in history." One hopes this is indeed the case, and that we are having the "dress rehearsal" for a performance we hope never takes place. ■

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Skin Infections in Travelers

By Lin H. Chen, MD

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Dr. Chen reports no financial relationships relevant to this field of study.

Synopsis: *Skin and soft-tissue infections are significant travel-related dermatologic conditions and commonly are associated with insect bites. These findings underscore the importance of bite prevention.*

Source: Hochedez P, Canestri A, Lecso M, et al. Skin and soft tissue infections in returning travelers. *Am J Trop Med Hyg* 2009;80(3):431-4.

The authors from Paris, France, described 60 adult travelers diagnosed with skin and soft-tissue infections (SSTI) seen between January 1, 2006, and August 30, 2007. Males comprised 63%, the mean age was 42 years, and the median duration of stay abroad was 15 days. The majority of cases developed lesions abroad (73%), whereas the remaining cases developed lesions after a median of 3 days after return. The majority of patients had traveled to Africa (57%), followed by Asia (10%), South America (8%), Indian Ocean (8%), Pacific (8%), Caribbean (7%), and North America (2%). Tourism was the most common reason for travel (68%), followed by business (18%), visiting

friends or relatives (10%), expatriates (3%).

The most common clinical presentations were impetigo (35%) and cutaneous abscesses (23%), followed by ecthyma (18%), cellulitis (18%), and furuncles and folliculitis (5%). The predominant affected area was a lower limb (75%). *Overall, 57% of patients had a history of insect bites in the same area of SSTI, including mosquitoes, spiders, fleas, and horseflies.* Among those with bacterial isolates, 43% had *Staphylococcus aureus*, 34% had group A β-hemolytic *Streptococcus* infections, and 23% were infected with both organisms. Panton-Valentine leukocidin was present in 4 patients with severe infection. No methicillin-resistant *S. aureus* (MRSA) was identified. Infection required hospitalization in 2 patients with cellulitis and surgery in 5 patients for abscesses.

■ **COMMENTARY**

Skin and soft-tissue infections are common health problems associated with travel. A recent analysis of international travelers presenting to travel clinics in the GeoSentinel Surveillance Network found that among 4,594 diagnoses reported after travel, 18% were dermatologic; 6.8% of the dermatologic diagnoses were superinfected insect bites, and 12.8% were attributed to pyodermas (cellulitis, skin abscess, erysipelas).[1] A study from the same French unit covering November 2002 to May 2003 reported 35 cases of SSTI (21 infectious cellulitis and 14 pyoderma) among 165 travelers who returned from the tropics.[2] The Hochedez study focuses on SSTI and presents informative results regarding adult travelers. The study excluded travelers younger than 15 years of age and patients who had impetiginized scabies and marine envenomation. Therefore, we cannot draw conclusions regarding SSTI in pediatric travelers or in travelers with marine exposures.

The high proportion of patients with SSTI who reported a history of insect bites highlights the need for bite prevention. The predominance of *S. aureus* and group A β-hemolytic *Streptococcus*, the most common pathogens in ordinary skin infections, speaks to the importance of intact skin in the prevention of SSTIs. The study reassures that to date, MRSA is not a common pathogen associated with SSTI in such travelers. However, the increasing incidence of community-acquired MRSA globally portends an emerging infection with travel association.

Panton-Valentine leukocidin (PVL) is a cytotoxin produced by *S. aureus* and causes severe necrosis, leads to high rates of transmission, and has been reported in travel-associated SSTI.[3] The presence of this gene in *S. aureus* indicates increased virulence, resembling methicillin-resistant *S. aureus*.[4] Hochedez, et al. reported that 27% PVL-positivity in their isolates of *S. aureus*, including an isolate from a woman who returned from Ivory Coast with recurrent infections and later led to infection in a male companion.

The key messages of the report by Hochedez et al are: bacterial infections of skin and soft-tissue contribute significant morbidity; insect bites predispose travelers to these problems; bite prevention and self-treatment of bacterial superinfection should be discussed; and consider checking for the presence of PVL in *S. aureus* isolates associated with virulent or recurrent infections. Prevention of the leading causes of dermatologic problems in travelers should include insect bite avoidance. Although clinicians evaluating returned travelers should consider the exotic diagnoses such as cutaneous larva migrans, leishmaniasis, and African tick bite fever, they must also suspect common, ubiquitous bacterial pathogens. ■

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Ciguatera Fish Poisoning

By Philip R. Fischer, MD, DTM&H

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Synopsis: *Ciguatera fish poisoning is caused by eating reef fish contaminated by algae-produced toxins — even when fish look normal and have been handled and cooked appropriately. Symptoms include neurologic and gastrointestinal abnormalities and can persist for months.*

Source: Langley R, Shehee M, MacCormack N, et al. Cluster of ciguatera fish poisoning — North Carolina, 2007. *MMWR* 2009;58:283-285.

AMBERJACK FISH CAUGHT OFF THE FLORIDA KEYS, distributed via Atlanta, Georgia, and sold at a fish market in North Carolina were linked to bothersome symptoms in nine individuals. Within a few hours of cooking and eating the fish, the index couple developed diarrhea followed by abnormal temperature and skin sensations. Both improved with the administration of intravenous mannitol.

Seven other people who, at a separate dinner party, ate filets of amberjack fish from the same market also became ill 4-48 hours (median 12 hours) after ingestion of the fish. They reported abnormal skin sensations, joint pains, weakness, shakiness, and/or fatigue. Three had recurrent or worsened symptoms after alcohol consumption. Six of the seven who were sexually active had pain with intercourse (on ejaculation for males, with a burning sensation that lasted up to three hours for females) that recurred for as long as one month. In all nine patients, some symptoms persisted for at least a month; six had resolution of symptoms by six months; and two still had abnormal skin sensations a year after the implicated amberjack meal. Cooked fish was positive for ciguatoxin. One woman was breastfeeding at the onset of symptoms and had no detectable toxin in subsequent breast milk samples.

■ COMMENTARY

Ciguatoxins are fat-soluble polyether compounds with potent effects on sodium channels.[1] Carnivorous reef fish such as barracuda, amberjack, red snapper, and grouper become contaminated when they eat herbivorous fish that have ingested *Gambierdiscus algal* dinoflagellates. These algae usually grow in association with coral reefs. The toxin is unrelated to apparent fish health or appearance and, being heat-stable, is not inactivated by cooking.

Ciguatoxins contaminate fish in warm waters, especially in Caribbean and Pacific areas but also in the Indian Ocean. There are multiple specific toxins, but all seem to cause both gastrointestinal and neurologic symptoms. Nonetheless, Caribbean poisoning is predominantly linked to gastrointestinal symptoms while Pacific poisoning is associated with more prominent neurologic findings. Sometimes, the severity of clinical symptoms seems to relate to the amount of toxin ingested, and toxin is most concentrated in fish viscera and gonads. The incidence of ciguatera fish poisoning varies from less than 1 per 10,000 per year in Reunion Island, to 1 per 170 in parts of the Caribbean to 1 per 5,850 in some Pacific islands (such as French Polynesia).[2] In fact, 70% of people living on some Pacific islands are thought to become symptomatic sometime during their lives.[2] Globally, it is estimated that 50,000 or more individuals likely are affected each year.[2]

The diagnosis of ciguatera fish poisoning hinges on clinical recognition of key features. Even in endemic areas, however, a third of physicians do not properly diagnose a classic case of ciguatera fish poisoning.[2] Vomiting and diarrhea beginning within hours of ingestion of warm water reef fish may be associated with abdominal pain and should raise suspicion of ciguatera fish poisoning; these gastrointestinal effects usually resolve within a few days. Cardiovascular complications such as bradycardia and hypotension occur early in the course of poisoning in only a small number of affected patients and are amenable to fluid resuscitation. Potential neurologic symptoms typically occur earlier in the course of the illness in Pacific Ocean areas, but often follow the initial vomiting and diarrhea in people affected by Caribbean fish. Common neurologic symptoms include parasthesias (with tingling and/or numbness, especially peripherally), itching, myalgia, arthralgia, and fatigue. A specific finding in many people with ciguatera toxicity is that of "temperature reversal" or "cold allodynia"; subjects sense burning hot pain when touching cold water or a cold object.[3] Neuropsychiatric symptoms seem more common when toxicity occurs in the Indian Ocean but might at least sometimes represent consequences of non-toxin-related concurrent health problems. While painful intercourse previously had been reported, the current series illustrates the possibility of toxins causing frequent, persistent pain with intimate sexual activity.

As experienced by some of the North Carolina patients, subsequent ingestion of alcohol, even after initial symptoms have resolved, can cause repeated ciguatera symptoms. Similarly, recurrences also have been associated with later ingestion of non-contaminated fish, nuts, caffeine, and some meats.[2] The reasons for this are not clear, but it has been suggested that some dietary products might trigger changes in fat metabolism and release residual toxin from human fat cells where it is being stored.[2] In other subjects, symptoms can persist for months or years without ever fully resolving.

Management requires careful supportive care, and fluid resuscitation may be necessary when gastrointestinal fluid losses are excessive. Mannitol is reported to be helpful, as noted in the index couple in the current report. A wealth of experience points to the value

of intravenous mannitol in the treatment of ciguatera fish poisoning, but a randomized, controlled trial found no benefit to this treatment.[4] It is not clear, however, whether mannitol was ineffective and should not be used[3] or whether the study was flawed in the ways mannitol administration was timed and in the manner by which results were analyzed.[2] Many experts still would suggest that mannitol (0.5-1.0 mg per kg body weight, intravenously over 30-45 minutes with repeated doses several hours later if symptoms recur) be used when ciguatera fish poisoning is recognized within three days of ingestion of the contaminated fish. Experiential evidence (without controlled trials) suggests that amitriptyline (and even selective serotonin reuptake inhibitors) can help with persistent pains that follow ciguatera fish poisoning.[2]

Fortunately, ciguatera fish poisoning rarely is fatal. Similar shellfish-related toxicities, such as neurotoxic shellfish poisoning and paralytic shellfish poisoning, more frequently are fatal. Puffer fish poisoning, common in Japan and often fatal, is caused by a tetrodotoxin that, like ciguatoxin, affects sodium channels.[3] ■

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Unanticipated Hepatitis Cases in Travelers

By Maria D. Mileno MD

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Dr. Mileno reports no financial relationships relevant to this field of study.

Synopsis: *Not all cases of hepatitis in travelers are viral, and the travel medicine provider must be aware of those unanticipated causes of hepatitis that can challenge practitioners during diagnosis.*

Sources: Senn N, Genton B. Acute hepatitis A in a young returning traveler from Kenya despite immunization before departure. *J Travel Med* 2009;16:72-73.

Christl SU, Seifert A, Seeler D. Toxic hepatitis after consumption of traditional kava preparation. *J Travel Med* 2009;16: 55-56.

RECENTLY PUBLISHED CASES OF HEPATITIS AMONG travelers describe a hepatitis patient's evaluation suggesting incomplete protection against hepatitis A following vaccination and unexpected toxicity from an interesting cultural experience. Both of these cases offer some issues for travel medicine practitioners to consider.

A 25-year-old man visited a travel clinic on January 8 to prepare for trip to Mombasa. He received Tdap, polio, MMR, and hepatitis A vaccines and had a prior history of yellow fever vaccine and a hepatitis B vaccine series. He received oral doxycycline for malaria prevention and stayed in a resort hotel from from January 8 until early February. On February 18, he presented with fever, myalgias, and headache. His physical examination was unrevealing, specifically without scleral icterus or abdominal tenderness.

Pertinent laboratory abnormalities included a serum AST 208 and ALT 320, positive hepatitis B surface antibody, and negative hepatitis C antibody.

His hepatitis A IgM antibody was positive but without quantitative antibody titer reported. HIV serology was negative. The authors reported this case as one of mild acute hepatitis A despite prior vaccination. His symptoms and laboratory abnormalities resolved spontaneously within several weeks.

A 42-year-old healthy male spent his 20-day honeymoon on the Samoan Islands. He presented 3 weeks later with weakness, loss of appetite, and jaundice. Although he admitted to modest alcohol consumption of 1 drink daily, he denied any medication or illicit drug use. On physical examination, he appeared weak, with normal nutrition status and normal temperature. He had florid scleral icterus and jaundice of the skin. His liver span was normal but pain was elicited on palpation. Significant laboratory abnormalities included serum AST 1602, ALT 2841, gamma GTP 121, LDH 420, and alkaline phosphatase 285. The total bilirubin 9.3 mg/dL, mostly direct, eventually rose to 31 mg/dL. He had negative serologies for hepatitis A, B, C, CMV, and EBV. The CBC, coagulation tests, and protein electrophoresis were normal, the serum ferritin of 1531µg/L was elevated, ceruloplasmin was normal but with increased urine copper excretion; genetic testing for hemochromatosis was negative. Pursuit of autoimmune causes of acute liver failure showed negative values for the following

antibodies: ANA, anti-smooth muscle, anti-liver/kidney microsomal, anti-soluble liver antigen, and anti-mitochondrial antibodies. Hepatic imaging by abdominal ultrasound revealed a hyperechoic liver with normal biliary ducts and thickened gallbladder wall; one 15 mm lymph node was noted in portal area. Histopathology on the liver biopsy showed infiltration of portal fields with lymphocytes and eosinophilic granulocytes, necrosis of hepatocytes, and swollen Kupffer cells consistent with drug-induced or toxic liver injury. Upon further questioning about his activities, the patient admitted he repeatedly participated in kava ceremonies and consumed a total volume of 2-3 liters of traditional kava preparations.

■ COMMENTARY

The first case might illustrate one potential illness that is a threat for many individuals who are exposed to hepatitis A sooner than 2 weeks following immunization. Most cases are probably asymptomatic. It is somewhat more difficult to diagnose acute hepatitis A following vaccination, and it would have been useful to determine quantitative titers of hepatitis A antibodies. Were they greater than 20 mIU/mL, this simply would have suggested seroconversion from vaccination, although the hepatic enzyme elevations would remain unexplained. Had the authors pursued HAV in stool samples by electron microscopy or PCR determinations, they might have presented a far stronger case. One might also question whether testing for acute hepatitis E virus infection should have been performed before attributing this case to hepatitis A infection following immunization.

Few cases of acute hepatitis A following immunization have been reported; most occurred greater than 1 year after immunization. Studies performed during epidemics suggest that patients need 14 days to achieve full protection following immunization. Damme et al published seroconversion rates of 80% after 2 weeks and 99% after 4 weeks.[1] It is possible that numerous individuals already have partial protection, given that the virus is so common. Hepatitis A vaccination is highly effective and should be given with confidence. However, practitioners also should inform travelers about incomplete hepatitis A protection due to last-minute vaccination, encourage visits 4 weeks prior to departure, and remind travelers that attention to simple hygiene and water precautions remains very important in hepatitis A prevention. More study is probably needed regarding vaccination for both the immunocompromised and elderly in whom immune responses are not as robust.

Kava is an esteemed mind-altering agent central to culture and custom in Oceania. The beverage is prepared from roots of the plant *Piper methysticum*. Kava has a key role in social ceremonies. It is usually the only way to welcome honored visitors. A former Pope, John Paul II, drank it with the Fijian prime minister and guests during the his visit to Fiji in 1986. Ceremonies mark special events such as marriages and births. In Hawaii, naming of 1-year-old children and initiating young girls into Hula and chanting are accompanied with a kava celebration in addition to use for relieving stress and remedying illnesses.[2,3]

In Fiji, it is believed that kava ceremonies also allow participants to communicate with the supernatural. Western descriptions of kava ceremonies date to the travels of Captain Cook. Kava "is made in the most disgusting manner that can be imagined. The root is cut small and the pieces chewed by several people who spit the macerated mass into a bowl where water of coconuts is poured upon it and they swallow this nauseous stuff as fast as possible." The effect it delivers seems to make this worthwhile. "It gives a pleasant warm and cheerful but lazy feeling, sociable, though not hilarious or loquacious; the reason is not obscured. The head is affected pleasantly; you feel friendly, not beer sentimental; you cannot hate with kava in you. Kava quiets the mind; the world gains no new color or rose tint; it fits in its place and in one easily understandable whole."[4]

Higher product potency was noted if virgin women chewed the roots and if the plant were grown on the island of Vanuatu. Presbyterians found this all entirely unacceptable.[4]

These days, a more sanitary preparation method is used, which involves grinding and grating instead of chewing and spitting. The chemistry of the active ingredients, the kavalactones, also has been well studied. They have properties as local anesthetics. Sedative and analgesic agents along with pill formulations have been available and widely used. Purported uses cited all over the Internet suggest use in treatment of urinary tract infections, premenstrual syndrome, headaches, and as an energy-boosting aphrodisiac, a cure for whooping cough, asthma, tuberculosis, and gonorrhea. Unlike benzodiazepines, kava's effectiveness does not diminish over time.[2,3]

In 1908, Thompson described kava's adverse events. With cumulative use, "the body becomes emaciated. The skin becomes dry and covered with scales especially the palms, soles, forearms and shins. Appetite is lost. Sleep is disordered. Eyes become bloodshot. There are pains in the pit of the stomach. The drinker sinks into unwholesome lethargy."[4] One coconut shell-full contains approximately 250 mg of the active ingredient. Consumption of more than 3-4 g is highly associated with adverse findings, as described in this case report.

In 2002, *MMWR* published an advisory against kava

use, when even mild usage was reported to cause hepatitis and liver failure requiring liver transplant in 2 U.S. cases and in 11 users worldwide.[5] Some countries have banned kava-containing medical products. NIH studies in the division of Complementary and Alternative Medicine are ongoing. ■

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CME Questions

9. Which of the following statements regarding novel influenza A H1N1 and air travel is *incorrect*?
   a. All ill persons should avoid travel.
   b. Proximity within the cabin to a coughing ill person increases risk of illness.
   c. If a person develops influenza-like illness during a flight, he or she should be isolated if possible and provided a mask.
   d. Laminar airflow in modern aircraft and use of HEPA filters reduce risk of airborne respiratory pathogens.
   e. Seating in the back of the cabin poses the greatest risk of respiratory illness.

10. Which of the following statements is true regarding dermatologic problems in travelers?
    a. They are typically uncommon but when they occur, they usually are caused by parasites.
    b. They can be associated with bacterial pathogens as well as parasites from the tropics.
    c. They are never associated with Panton-Valentine leukocidin-containing *S. aureus*.
    d. They are not amenable to prevention and self-treatment for bacterial superinfection of insect bites.

11. Ciguatera fish poisoning:
    a. often presents with vomiting and/or unusual superficial sensation
    b. occurs after eating freshwater fish in northern latitudes
    c. is prevented by avoiding ingestion of raw rather than cooked fish
    d. frequently is fatal

12. Acute hepatitis A infection in travelers is likely to be confused with each of the following syndromes *except*:
    a. acute hepatitis E infection
    b. excessive kava ingestion
    c. carbon tetrachloride poisoning
    d. ciguatera fish poisoning
    e. infectious mononucleosis

Answers: 9. e; 10. b; 11. a; 12. d

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*.

Guidance on the Appropriate Use of NSAIDs

In this issue: NSAIDs in the elderly; managing GI and CVD risk with NSAIDs; low-dose naltrexone and fibromyalgia; treating glucocorticoid-induced bone loss; FDA Actions.

NSAIDs and dementia

Chronic use of nonsteroidal anti-inflammatory drugs (NSAIDs) in the elderly may increase the risk of dementia and Alzheimer's disease according to a new study. This is in contrast to previous studies that suggested that NSAIDs may actually be neuroprotective. The current study from Seattle looked at members of Group Health who were age ≥ 65 years (median, 74.8 years) and free of dementia. Patients were followed for up to 12 years to identify dementia and Alzheimer's disease. Of the 2736 patients studied, 351 (12.8%) were heavy users of NSAIDs at enrollment and another 107 became heavy users during follow-up. Over the course of the study 476 individuals developed dementia including 356 who developed Alzheimer's disease. Those defined as heavy NSAID users showed an increased incidence of dementia (hazard ratio [HR], 1.66; 95% confidence interval [CI], 1.24-2.24) and Alzheimer's disease (HR, 1.57; 95% CI, 1.10-2.23). The authors suggest that this study looked at an older cohort than previous studies. Decreased rates of dementia seen in the previous studies may have reflected a delay in onset of dementia, which may explain the increased incidence seen in the older patients in this study (*Neurology* 2009 April 22; epub ahead of print). ■

GI and CVD risk with NSAIDs

In a related story, the Canadian Association of Gastroenterology Consensus Group has published guidelines on use of long-term NSAIDs in patients at risk for GI bleeding and cardiovascular disease. The guideline includes the recommendation that NSAIDs should always be used at the lowest effective dose for the shortest possible duration of treatment and that patients should be evaluated for the need for gastroprotective strategies and cardiovascular risk. For patients at low GI risk but high cardiovascular risk, the group recommends naproxen because of potentially lower cardiovascular risk than other NSAIDs or COX-2 inhibitors. For patients at high risk for GI side effects and low cardiovascular risk, a COX-2 inhibitor alone or traditional NSAIDs with a PPI offers similar protection. For patients at very high risk for GI bleeding, a COX-2 inhibitor plus a PPI is the safest option. In patients with both GI and cardiovascular risks, NSAIDs should be avoided if possible, but if anti-inflammatories are needed, and the patient is already on aspirin, the recommendations included naproxen plus a PPI if cardiovascular risk is the main concern or a COX-2 plus a PPI if GI side effects are the primary concern (*Aliment Pharmacol Ther* 2009;29:481-496). ■

Low-dose naltrexone and fibromyalgia

Perform a Google search of "low-dose naltrexone"

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and you will find a myriad of anecdotal testimonies to the benefits of the drug in a wide range of diseases including fibromyalgia. Now a small study suggests that naltrexone may be of some benefit in this difficult condition. Naltrexone (not to be confused with naloxone) is an opioid receptor antagonist used primarily for treatment of alcohol dependence and opioid dependence. Because of multiple internet reports of benefit in patients with fibromyalgia, researchers from Stanford performed a single-blind, placebo-controlled crossover study of 10 patients with moderately severe fibromyalgia who were not on opioids. The dose of naltrexone used was 4.5 mg per day, which is less than 10 times lower than the dose used for addiction (50 mg per day). Patients on active treatment reported a 32.5% reduction in fibromyalgia symptoms compared to baseline vs a 2.3% reduction for placebo (P = 0.003 vs placebo). Side effects, which included insomnia and vivid dreams, were rare. Interestingly, patients with higher sedimentation rates had the greatest reduction in symptoms and best response to low-dose naltrexone. The authors hypothesize that low-dose naltrexone may inhibit the activity of microglia and reverse central or peripheral inflammation, thus reducing symptoms of fibromyalgia, although more studies are needed. They also suggest that naltrexone can be used in addition to other medications commonly used for fibromyalgia (*Pain Med* 2009 April 22; epub ahead of print). ■

Treating glucocorticoid-induced osteoporosis

For patients with glucocorticoid-induced osteoporosis, a once-yearly infusion of zoledronic acid is as effective as daily risedronate for the prevention and treatment of bone loss according to a new study from *Lancet*. In a 1-year, international, randomized, double-blind, placebo-controlled, non-inferiority study, 833 patients with glucocorticoid-induced osteoporosis were randomized to receive zoledronic acid 5 mg as a 100 mL IV infusion over 15-20 minutes on day 1 plus oral placebo or 5 mg of risedronate daily and 100 mL IV placebo infusion on day 1. Patients were allocated to a prevention or treatment subgroup depending on the duration of glucocorticoid use preceding study. Zoledronic acid infusion was non-inferior and superior to risedronate for increase of lumbar spine bone mineral density in both the treatment (P = 0.001) and prevention groups (P < 0.0001), respectively. Adverse events were more frequent in patients given zoledronic acid primarily because of increased flu-like symptoms within the first 3 days after the infusion. The authors conclude that a single 5 mg intravenous infusion of zoledronic acid is non-inferior and possibly more effective and more acceptable to patients than 5 mg of oral risedronate daily for prevention and treatment of bone loss associated with glucocorticoid use (*Lancet* 2009;373:1253-1263). An accompanying editorial suggests that once-yearly zoledronic acid seems to have obvious advantages over an oral regimen but the long-term safety is still unknown and also raises the question of whether anabolic drugs, such as teriparatide, which stimulate bone formation by acting on osteoblasts and osteocytes, might eventually be a better option (*Lancet* 2009;373:1225-1226). ■

FDA Actions

Plan B, the so-called "morning after pill" will soon be available to women age 17 and older without a prescription. Previously the FDA and the Bush administration had limited the access of the drug to women 18 and older but a U.S. district judge ruled in March that the older age limit was "arbitrary and capricious." The judge also directed the agency to evaluate clinical data to determine whether there should be any age restrictions on use of the drug. The FDA has no plans to appeal the court's decision. Duramed Pharmaceuticals must file paper work with the FDA, a process that is expected to take 30 days. Plan B is levonorgestrel in a 2-pill pack, the first to be taken within 72 hours of unprotected intercourse and the second pill 12 hours later.

The FDA has approved a new TNF-alpha blocker monoclonal antibody for the treatment of rheumatoid arthritis, active psoriatic arthritis, and active ankylosing spondylitis. Golimunab is given once a month as a subcutaneous injection in combination with methotrexate for rheumatoid arthritis. It may be used with or without methotrexate for psoriatic arthritis and as monotherapy for ankylosing spondylitis. As with all TNF-alpha blockers, the FDA is requiring a risk evaluation mitigation strategy (REMS), which includes a medication guide for patients and a communication plan for physicians regarding potential side effects. Also similar to other drugs in this class, golimumab will carry a boxed warning regarding the risk of tuberculosis and invasive fungal infections. Golimumab was developed by Centocor Ortho Biotech, a division of Johnson & Johnson. The drug will be marketed under the trade name Simponi™. ■