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Monkeypox in the Post-Smallpox Vaccination Era

ABSTRACT & COMMENTARY

By Brian G. Blackburn, MD, and Michele Barry, MD, FACP

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Dr. Barry serves as a consultant for the Ford Foundation, and her program receives funding from the Johnson & Johnson Corporate Foundation. Dr. Blackburn reports no financial relationships related to this field of study.

Synopsis: *Monkeypox incidence increased 20-fold from the early 1980s to 2005-07 in the Democratic Republic of Congo (DRC). The risk of monkeypox was higher in younger and unvaccinated individuals, and likely indicates that decreasing immunity in the population three decades after the cessation of smallpox vaccination campaigns is contributing to the resurgence of this disease.*

Source: Rimoin AW, et. al. Major increase in human monkeypox incidence 30 years after smallpox vaccination campaigns cease in the Democratic Republic of Congo. *PNAS* 2010;37:16262-7.

MONKEYPOX IS AN ORTHOPOXVIRUS RELATED TO VARIOLA THAT CAUSES A CLINically similar illness to smallpox, albeit less severe.[1] Although initially described in primates, rodent species such as African squirrels, giant pouched rats, and dormice appear to be the primary reservoirs in nature. Humans acquire the disease both from animals and human-to-human transmission. Although an outbreak was reported in the United States in 2003 related to the importation of exotic pets, monkeypox has been found in nature only in Central and West Africa.[1,2]

Smallpox vaccination confers about 85% protection against monkeypox, but vaccination campaigns ceased following the eradication of this disease.[1] Although systematic surveillance for monkeypox had been ongoing in the immediate post-smallpox vaccination era within some parts of Africa, such surveillance has not been well maintained subsequently. Overall, the largest numbers of monkeypox cases have been reported from the DRC, and smallpox vaccination officially ended there in 1980.[1,3]

To better delineate recent monkeypox epidemiology and transmission, an active surveillance program was re-instituted during 2005-07 in areas within the DRC where monkeypox was known to be circulating. A suspected case of

human monkeypox was defined as a patient with a fever accompanied by a vesicular-pustular rash. Cases were considered confirmed if monkeypox virus was detected within scab or vesicular fluid when tested by polymerase chain reaction (PCR).

From 2005-07, 760 confirmed cases of monkeypox were detected in nine health zones in the central DRC, where the annual crude incidence rate was 5.5 cases per 10,000. The mean age of case-patients was 12 years, 62% were male, and cases were more commonly found in forest than savannah regions. In one representative health zone with relatively comparable disease surveillance activity in the 1980s and 2000s, the annual monkeypox incidence increased from 0.7 to 14.4 per 10,000, representing a 20-fold increase.

Overall, the risk of human monkeypox was inversely associated with age and smallpox vaccination. More than 92% of case-patients were born after 1980, and only 4% of case-patients had evidence of prior smallpox vaccination, compared with 26% of the general population. Vaccinated persons who were born before 1980 had a five-fold lower risk of monkeypox compared with unvaccinated persons (0.8 vs. 4.1 per 10,000). In this group, vaccine efficacy was estimated to be 81% (95% CI 68–88%).

■ COMMENTARY

Human monkeypox is a zoonosis that occurs primarily in remote villages of Central and West Africa in proximity to tropical rainforests where there is far more frequent contact with infected animals. The use of reservoir animals as food may be an important source of transmission to humans, since contact with sick animals has resulted in transmission through respiratory droplets.

The incubation period for monkeypox is about seven to 17 days, and the illness begins with fever, headache, and myalgias. Lymphadenopathy is prominent and is the principal distinguishing characteristic from smallpox; it occurs coincidentally with prodromal fever prior to the rash. Laboratory diagnosis includes identification through PCR, culture, or blood serology. Currently, there is no proven, safe treatment for monkeypox, and the Centers for Disease Control and Prevention (CDC) recommends that persons investigating monkeypox outbreaks and involved in the care of infected individuals receive smallpox vaccination to protect against monkeypox. Persons who have had close contact with individuals or animals that have monkeypox should also be vaccinated up to 14 days after exposure. CDC does not recommend pre-exposure vaccination for veterinarians, veterinary staff, or animal control officers unless such persons are involved in field investigations. No data are available on the effectiveness of cidofovir in treatment of human monkeypox. However, cidofovir has proven anti-monkeypox activity both in vitro and in animal studies.[4]

Three decades after the eradication of smallpox, waning population immunity as a result of the elimination of natural disease and the cessation of smallpox vaccination programs caused the unintended effect of reducing immunity to related monkeypox virus. This study demonstrates this effect dramatically through the recent increase in the incidence of monkeypox in the DRC, the preponderance of the infection in the young and unvaccinated, and the less dramatic increase among populations with higher rates of smallpox vaccination. Even 30

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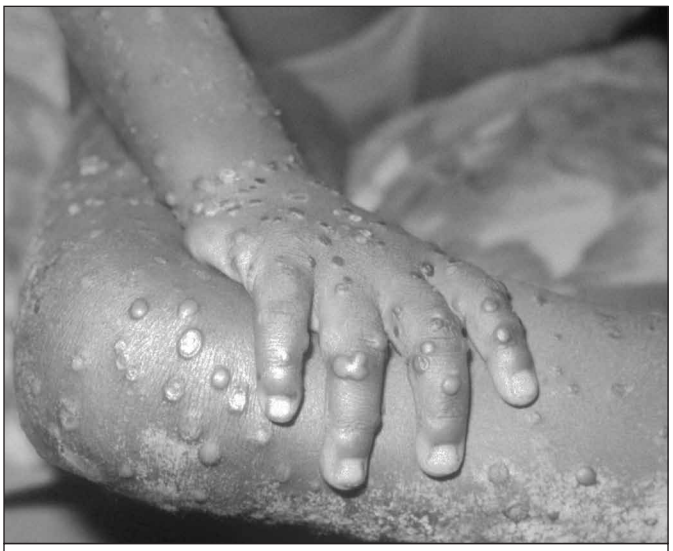
Figure. Monkeypox



Source: Centers for Disease Control and Prevention

years after vaccination, cross-protection for monkeypox appears to be significant.

It is also possible that behavioral factors have driven some of the epidemiological changes seen in this study. As the authors indicate, contact with animal reservoir species is an important factor in many human monkeypox virus infections. In the DRC, contact of local populations with reservoir species harboring monkeypox virus has probably intensified since 1980, increasing the chances of animal-to-human infection. Monkeypox continues to occur almost exclusively in rural villages in proximity to tropical rainforests. Continued deforestation may favor an increase in human exposure to squirrels and other suspected reservoir species. Additionally, war and resultant widespread poverty have forced residents to rely increasingly on monkeys, squirrels, and other rodents for sustenance, all potential sources of monkeypox infection. Additionally, human-to-human transmission also may have increased, as entire households are now vaccine-naïve. Given the high attack rate and secondary transmission rates for this virus, intra-household transmission is now much more likely to occur, particularly between parents and children.

These findings have important implications. Monkeypox is a serious disease, with mortality rates as high as 10% in some series.[1] Although the eradication of smallpox represents a public heath triumph, the re-emergence of monkeypox serves as a reminder that unanticipated consequences can result — even from the best of intentions. If monkeypox were to establish itself in a new area, the lack of natural immunity in animals and humans, particularly among the young, could predispose to large outbreaks and a public health threat. Already, within endemic foci of Africa, the disease has largely gone unmonitored, possibly causing increased morbidity and mortality in recent years. Improved surveillance and epidemiological analysis are sorely needed to better assess the public health burden of this infection, and to develop strategies for reducing the spread of infection. ■

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New Pathways to Hepatitis E Infection

ABSTRACT & COMMENTARY

By Lin H. Chen, MD

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

Synopsis: *Hepatitis E virus (HEV) infections cause hepatitis outbreaks in developing countries, and travelers must exercise caution regarding food and water. HEV infection has also been increasingly identified in developed countries, associated with consumption of game meat or undercooked pork products, and infections can lead to chronic hepatitis in immunocompromised patients.*

Source: Teshale EH, et al. The two faces of hepatitis E. *Clin Infect Dis* 2010;51:328-334.

Teshale and colleagues reviewed hepatitis E virus (HEV) infections and the two distinct presentations associated with this virus infection. HEV was initially recognized in the 1980s, but a number of outbreaks have been identified since the 1950s in India, Kashmir, Mexico, Ethiopia, China, Vietnam, Sudan, and Uganda. In comparison, only sporadic cases have occurred in industrialized countries. One presentation occurs during outbreaks in developing countries, predominantly caused by genotype 1 and sometimes genotypes 2 and 4; this syndrome is associated with high morbidity and mortality among pregnant women and young children. The other presentation is an asymptomatic infection, usually with

genotype 3, and occurs in developed countries where the HEV seropositivity rate is 5-21%.

HEV belongs to the genus Hepevirus and is a non-enveloped RNA virus with at least 4 genotypes. HEV was initially considered a waterborne infection, but recent studies suggest additional transmission routes including transmission from person to person and via blood transfusions. Following exposure to the virus, the mean incubation period lasts 40 days (range 15-60 days), and infection leads to a wide range of presentations, from asymptomatic infection to fulminant hepatitis. Symptomatic HEV infection may present with jaundice, fever, hepatomegaly, malaise, and pruritus. Laboratory findings include elevated serum bilirubin, liver enzymes, and alkaline phosphatase levels. Case fatality rates in developing country epidemics range from 0.2-4%, but reach 10-25% in pregnant women, especially during the third trimester.

In industrialized countries, HEV genotype 3 appears to be prevalent, but only infrequently pathogenic. Some serological surveys have found high anti-HEV IgG seropositivity rates in the United States (21%) and Denmark, but much lower rates in other European countries and Japan. The disparity arises from variations in sensitivity and specificity of the assays used. HEV genotype 3 is considered a zoonosis of wild pigs, and consumption of wild or domestic pork seems to be associated with HEV infection in industrialized countries. However, numerous examples suggest additional modes of exposure, including the consumption of raw or undercooked shellfish.

Chronic HEV infection rarely occurs, yet cases have been reported in immunosuppressed patients such as transplant recipients, and chronic carriage may occur in HIV-infected patients. Reactivation of resolved HEV infection appears possible, as in a leukemia patient who underwent allogeneic stem cell transplantation. Severe disease from HEV may also be associated with underlying liver disease. Pregnant women and very young children are associated with high mortality in developing countries, in particular Central Asia and Africa.

The diagnosis of acute HEV infection can be established most reliably by nucleic acid amplification to identify HEV RNA in blood or stool specimens. Blood samples showed HEV RNA from about 2 weeks before to 1 week after the onset of jaundice, whereas stool samples are positive later than blood but last 2 weeks after blood samples become negative. Diagnosis can also be obtained serologically by the detection of anti-HEV IgM, which disappears over 4-6 months, or anti-HEV IgG, which may persist for more than a decade. Currently no antibody assay is approved by the U.S. Food and Drug Administration (FDA).

■ COMMENTARY

Autochthonous HEV infections are increasingly reported in Europe. In southwest England, testing for HEV IgG in patients with unexplained hepatitis and among blood donors identified 40 cases of autochthonous HEV (genotype 3). The disease affected predominantly elderly Caucasian males, was anicteric in 25% of the cases, and typically was self-limiting. Complications occurred in 6/40 patients, and 3 patients died, including 2 with previously unrecognized cirrhosis.[1] In this population, HEV peaked in the spring and summer and was silent in November-December. Seroprevalence increased with age and was 16% in blood donors, 13% in patients with chronic liver disease, and 20% in persons older than 60 years.[1]

A challenge in the diagnosis of HEV infection is the lack of standardization and accuracy among some diagnostic tests. A study that was published in the same issue of *CID* reported the performance of six immunoassays for detecting IgM antibodies to HEV. Drobeniuc et al. tested sera from patients with acute infection against each of the 4 genotypes and also those with nonacute HEV infections. They found wide variations in sensitivities, specificities, and lack of interassay consistency. The two in-house assays that were tested performed well. Among the commercial assays, the best performers were Diagnostics Systems with a sensitivity of 98% and specificity of 95.2%, and Mikrogen with a sensitivity of 92% and specificity of 95.6%.[2] The commercial assays from Immuno-Diagnostics and MP Biomedicals had lower sensitivities (82% and 72%, respectively) mainly due to poor detection of genotypes 2, 3, and 4.[2] These data indicate that a clinician evaluating a traveler for possible acute hepatitis E infection must consider the reliability of the diagnostic test being used. In the United States, HEV PCR is performed in some research settings, but this could be a confirmatory test to the immunoassays, if available.

We have learned much about HEV, but more questions remain. As summarized by Teshale et al., there are two distinct clinical pictures of HEV. The first is that of outbreaks in developing countries leading to high morbidity and mortality among pregnant women and young children, and the second is that of subclinical infections in developed countries whose sources of exposure await further elucidation.

Recently, Colson et al. conducted a case-control study in France on three cases of autochthonous hepatitis E and 15 family members. They found that figatellu, a traditional pig liver sausage dish often served raw and consumed widely in France, was a source of HEV infection. Tests for HEV IgG and IgM antibodies and HEV RNA were positive in 7 of 13 individuals who ate raw figatellu and 0 of 5 individuals who did not eat raw figatellu ($P = 0.041$).[3] HEV genotype 3 RNA was identified in 7 of

12 figatelli purchased in supermarkets, and statistically significant genetic links were found between the RNA sequences obtained from both patients and the figatelli.

Because of its association with chronic disease in immunocompromised hosts, a case-control study among solid-organ transplant recipients sought to identify risk factors for HEV infection and to characterize the infections through serological tests, virus quantification, and viral genotyping. Among 38 consecutive patients, all with genotype 3 infection, 22 (58%) developed a chronic infection. Serum liver enzymes were higher in the patients who cleared the virus than in those who developed chronic infections, but the anti-HEV IgG and IgM profiles and HEV RNA levels were similar. A logistic regression analysis found the only positive association with HEV infection was the consumption of game meat (68% of case patients vs 47% of control participants; odds ratio, 2.32; 95% confidence interval, 1.04-5.15).[4]

These recent data suggest that consumption of game meat or undercooked pork products is one route of exposure to HEV. Because HEV can lead to chronic hepatitis in immunocompromised patients, these individuals should avoid eating game meat or undercooked pork products to prevent the acquisition of HEV infection and the development of chronic hepatitis. ■

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Cholera Outbreak in Haiti — November 2010

ABSTRACT & COMMENTARY

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

Synopsis: *Cholera continues to claim lives in Haiti, where relief efforts focus on treatment of cholera cases, interventions to provide clean water and improve sanitation, and education of affected communities on safe water and hygiene.*

Source: Pan American Health Organization (PAHO/WHO) — Health Cluster Bulletin Cholera Outbreak in Haiti. http://new.paho.org/hq/index.php. Centers for Disease Control (CDC) Cholera Outbreak — Haiti, October 2010. *MMWR* 2010;59(43):1393-1432.

An outbreak of cholera is ongoing in Haiti. As of Nov. 10, 2010, the *Ministère de la Santé Publique et de la Population* (MSPP) of Haiti reported 12,303 hospital admissions and 796 deaths in six geographic departments. The causative agent has been identified as toxigenic *Vibrio cholerae* 01, serotype Ogawa, biotype El Tor by the National Laboratory of Public Health of the MSPP of Haiti and confirmed by the Centers for Disease Control and Prevention (CDC). Antibiotic susceptibility testing shows resistance to trimethoprim-sulfamethoxazole, furazolidone, naldixic acid, sulfisoxazole and streptomycin and susceptibility to tetracycline, ciprofloxacin, and kanamycin.

The outbreak began in the Artibonite department, a rural but densely populated area north of Port-au-Prince. Fears of spread to Haiti's capital have now been confirmed, with an estimated 278 hospital admissions and 10 deaths reported in Port-au-Prince as of Nov. 9, 2010. The first case near the capital was reported in a 3-year-old boy from Cité Soleil, a slum north of the city where many people live in cramped, unhygienic conditions without adequate sanitation.

In January 2010, Port-au-Prince and other nearby towns were devastated by a 7.0 magnitude earthquake, which is estimated to have killed more than 250,000 people and left another million displaced and homeless, many of whom are now living in temporary tented camps around the capital. The next assault was Hurricane Tomas, which killed another 21 people and left 6,610 people homeless in early November. The hurricane passed by without destroying these tented camps, but the heavy rains caused significant flooding, which likely will facilitate the spread of cholera.

The government and its partners are in the process of setting up 10 new cholera treatment centers, each with a capacity of 100-400 beds in addition to the eight centers already in operation in Port-au-Prince and the surrounding areas. In addition, many non-profit organizations from around the world are on the ground helping in Haiti to supply educational information, oral rehydration salts

(ORS), chlorine and other disinfection tablets, Ringers Lactate solution, and antibiotics in an effort to curb the outbreak.

■ COMMENTARY

Cholera is transmitted through fecal contamination of water and food. Infections are often asymptomatic or cause a mild gastroenteritis, but about 5% of infected persons develop a severe, dehydrating, acute watery diarrhea. The classic description is that of "rice water stools." Blood type O is associated with increased vulnerability to severe cholera (cholera gravis). The mainstay of treatment is rehydration, either with oral rehydration salts and, when needed, intravenous fluids and electrolytes, such as Ringers Lactate solution. Antimicrobial treatment is recommended for severe cases but does not play a role, nor should it be used, for chemoprophylaxis to prevent cholera on a mass scale.

Two types of oral cholera vaccines are available globally: 1.) Dukoral; and 2.) Shanchol and mORCVAX. The once-licensed oral, live, attenuated single-dose vaccine (CVD 103-HgR) is no longer produced. An injectable vaccine prepared from phenol-inactivated strains of *V. cholerae* is still made in several countries but is not endorsed by the WHO because of its short duration of protection and limited efficacy.

Dukoral consists of killed whole-cell *V. cholerae* 01 with purified recombinant B subunit of cholera toxoid (WC-rBS) and is available in more than 60 countries, but not the United States. To protect the toxin subunit from being destroyed by gastric acid, the vaccine must be given with a bicarbonate buffer. Primary immunization consists of 2 oral doses given 7 or more days apart for adults and children older than 6 years, with a booster dose after 2 years. Children 2-5 years of age should receive 3 doses 7 or more days apart, and Dukoral is not approved for children younger than 2 years.

Field trials in Peru and Bangladesh have shown that Dukoral oral cholera vaccine confers 85-90% protection for 4-6 months among all age groups. Protection declined rapidly in young children after 6 months, but remained at about 60% after 2 years for older children and adults.[1] Dukoral contains the recombinant B subunit, which is structurally similar to the heat-labile toxin of ETEC and in several studies has been shown to protect against this agent. In studies of travelers to cholera-endemic countries, 52% of travelers had short-term protection against diarrhea caused by ETEC, and the protective efficacy against a combination of ETEC and any other pathogen was 71%.[2,3]

Shanchol and mORCVAX are two closely related bivalent oral cholera vaccines that resulted from a technology transfer of the WC/rBS vaccine from Sweden to India and Vietnam. Shanchol will be produced for Indian markets and international use, and mORVAX is intended for domestic use in Vietnam. Both vaccines are based on serogroups 01 and 0139 and do not contain the recombinant B subunit (so they do not require a buffer); however, they do not confer protection against ETEC. Vaccine is administered in 2 liquid doses 14 days apart for persons older than 1 year of age with a booster after two years. Efficacy trials are ongoing, but an interim analysis of a large Shanchol study in Kolkata, India, showed a protective efficacy at two years of 67% among those who received 2 doses.[4] Since the recombinant subunit B is not in these vaccines, production costs are much lower, and Shanchol is estimated at $1 per dose.

With these effective oral vaccines, one might ask why cholera vaccine is not being shipped to Haiti to help with the outbreak. One big problem is the supply of oral cholera vaccine. There may be only 200,000 or so doses of Dukoral, which is the only oral vaccine prequalified by the WHO. The second problem is that unlike the ring vaccination strategy that was effective in smallpox (during which everyone infected with smallpox has symptoms), once a cholera outbreak is in progress, up to 80% of people may already be asymptomatic carriers. Also, at least two doses of vaccine separated by 7-14 days are needed, with several more weeks before immunity is established. The WHO and Pan American Health Organization (PAHO) quote the logistical aspects of delivering and monitoring cholera vaccination in the midst of a cholera outbreak as reasons why they focus on traditional cholera public health measures. That said, the possibility and feasibility of vaccinating some populations beyond the current outbreak zones in Haiti (pre-emptive vaccination) is under consideration. Of note, PAHO does not recommend vaccination of health care workers nor of its own staff or visiting expert consultants traveling to Haiti since person-to-person transmission is extremely rare.

The mainstay of cholera outbreak control, therefore, goes back to proven public health measures such as providing appropriate treatment to people with cholera, implementing interventions to improve water and sanitation, and mobilizing communities by educating people about hand washing and providing the basics of safe water, soap, and oral rehydration salts. Yet despite the efforts to provide safe water and improved sanitation globally, the number of cholera cases reported to the WHO in 2009 increased by 16%. Africa suffered the worst toll, with 217,333 of the 221,226 total cases and 4883 of the 4926 total deaths. Zimbabwe, Ethiopia, and the Democratic Republic of Congo had the most cases. Important steps toward global cholera control likely will need to include broadening the implementation of the existing oral cholera vaccines as well as continued research and development of newer cholera vaccines

with longer-lasting immunity. ■

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Potential Pediatric Pulmonary Parasites

ABSTRACT & COMMENTARY

By Phil Fischer, MD, DTM&H,

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

Synopsis: *Respiratory symptoms in immigrants and returned travelers can prompt consideration of several different parasitic pulmonary infections. In October 2010, two U.S.-based journals published case reports and photos of children with hydatid cysts in the lungs. Echinococcosis relates to close contact with dogs and is treatable by a combination of medical and surgical therapies.*

Sources: Ludmir J, Valliante WK, Kuskov SI, et al. Picture of the Month: Ruptured hydatid lung cyst. *Arch Pediatr Adolesc Med* 2010;164:973-975.

Kumar VA, Mehta A, Agara D. Actively motile larval forms in fluid aspirated from lung. *Clin Infect Dis* 2010;51:804-805, 865-866.

One month after being treated for "pneumonia," an 8-year-old boy from Botswana presented with a one-day history of fever, cough, and chest pain. He was tachypneic and had radiographic evidence of an encapsulated structure in the left chest containing an air-fluid level. A liver cyst was also noted on computed tomographic (CT) imaging. Three days later, he developed more acute respiratory distress with a pneumothorax. During thoracostomy, pleural thickening and a bronchopleural fistulae were identified. An hydatid cyst was removed via lobectomy. Typical *Echinococcus granulosus* structures were identified histologically. Post-operatively, he was treated with albendazole for three months.

A 7-year-old boy in India who was reportedly "inseparable from his pet dog" sought medical care with a two-week history of respiratory symptoms. A chest radiograph showed an effusion. Fluid was drained percutaneously, and a cyst was aspirated transthoracically. Active, motile parasites were identified in the cyst fluid; characteristic "mouth parts" of *Echinococcus granulosus* were seen under magnification. The boy was treated with albendazole for six weeks.

■ COMMENTARY

With widespread international travel, medical personnel who care for immigrants and returned travelers can expect to see parasitic infections they might otherwise have relegated to distant memories of medical school parasitology courses. As demonstrated by these two recently reported children, hydatid disease is still a real clinical problem to reckon with.

Echinococcus granulosus[1] is a global cestode tapeworm that usually lives in sheep (as the intermediate host of parasite larvae) and dogs (as the definitive host of adult parasites). Human infection most often occurs following ingestion of eggs from the feces of infected dogs, sometimes from close contact with contaminated muzzles and paws. The "hatched" parasites then cross the human intestinal lumen to gain access to the portal circulation and, eventually, the liver and/or lungs. In about 10% of infected children, other tissues are also involved. Multiple cysts are observed in about one-fourth of infected children. Cysts are often asymptomatic, but they can cause upper abdominal pain with nausea and vomiting. Rupture of a cyst can result in fever, abdominal pain, and allergic symptoms as serious as anaphylaxis. Pulmonary findings can also result from erosion or fistulization of a cyst into the airway. The diagnosis is based largely on historical findings associated with radiographic evidence of typical cysts. The disease may be staged by classification of the cyst. Serologic tests can be useful in confirming a diagnosis. Cyst rupture, even if associated with medical intervention, has provoked worsened symptoms, so the previous mainstay of treatment was surgical excision of an unruptured cyst. More recently, however, improved results have been seen using chemotherapy, such as albendazole. Then, depending on the number and nature of the cysts, treatment is instituted combining percutaneous aspiration, injection of a parasiticidal agent, and re-aspiration. Widespread eradication efforts involve alterations in sheep-slaughtering practices and treatment of dogs but have only been successful in Iceland, Tasmania, and New Zealand.

Beyond echinococcosis, other parasitic worms can also cause pulmonary findings in children.[2] Hookworm, picked up by skin contact with fecally contaminated dirt

or grasses, and Ascariasis, transmitted by the fecal-oral route, both have larval stages that pass through human lungs. Fever, cough, and wheezing can result, and eosinophilia often is found during the passage of larvae through the pulmonary system. Both mebendazole (100 mg by mouth twice daily for three days, same dose for children as for adults) and albendazole are effective for treatment. Pulmonary strongyloidiasis, transmitted by skin contact with contaminated soil but sometimes perpetuated by auto-reinfection, is occasionally complicated by bacterial superinfection. This occurs when bacteria carried by larvae penetrate the intestinal lumen and enter the human vascular system — a potentially fatal event. Severe disease is most common in immunocompromised patients, such as those receiving chemotherapy. Treatment with ivermectin or albendazole is helpful.

Young schistosomal parasites that develop in the human after skin contact with contaminated fresh water will also pass through the lungs en route to the establishment of adult worm infections in the vascular system. Symptoms can include fever, cough, respiratory distress, and eosinophilia one to two months following the initial infection. Praziquantel provides effective treatment of adult worms and can also help with early pulmonary infections. Paragonimiasis is contracted by eating raw, parasite-infected freshwater crabs and crayfish. It is associated with fever, cough, and even hemoptysis. Praziquantel is the treatment of choice.

Certainly, parents would prefer that their traveling children not develop infection with pulmonary parasites. Prevention of all these different infections, however, requires blocking skin contact with soil and grasses through the use of shoes and clothing, avoiding contact with fresh water in areas where schistosomes live, and the "usual" remembering to apply good hand hygiene, eating only well-cooked foods, and drinking only pure or treated beverages. The elimination of all contact with parasites can be very difficult, and the development of respiratory symptoms following international travel should prompt health care providers to consider the possibility of parasitic lung infections. Of course, tuberculosis should always be part of the differential diagnosis. ■

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CME Questions

9. Monkeypox incidence is increasing in the Democratic Republic of the Congo, and it is likely primarily due to:
   a. importation to Africa of animals infected with the virus
   b. waning immunity in humans following the cessation of smallpox vaccination
   c. aging of the population and more cases in the elderly
   d. introduction of new vectors
10. Which of the following trip exposures is of little significance for hepatitis E acquisition?
   a. a hunter who consumed bear meat from his hunting trip in Canada
   b. a traveler returning from southern France who ate uncooked local sausages
   c. a kidney-transplant patient who visited England on a 1-week guided tour
   d. a backpacker who visited India for several months
11. Which of the following statements regarding cholera is *incorrect*?
   a. person-to-person transmission is uncommon
   b. the mainstay of cholera treatment is rehydration
   c. antibiotics are recommended for mass chemoprophylaxis
   d. the number of cholera cases reported in Haiti is increasing
12. Which of the following is a correct epidemiologic association?
   a. echinococcosis: sushi
   b. ascariasis: aerosols
   c. schistosomiasis: pigs
   d. paragonimiasis: crayfish

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: 9. b; 10. c; 11. c; 12. d

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.*

Tiotropium for Uncontrolled Asthma

In this issue: Tiotropium for uncontrolled asthma, sibutramine pulled from market, incidence and mortality data from WHI, FDA Actions.

Tiotropium for uncontrolled asthma

Tiotropium, a long-acting anticholinergic inhaler, is approved for treatment of chronic obstructive pulmonary disease. A new study suggests that it may also be effective for patients with asthma.

In a study of 210 adults with asthma with inadequate control with inhaled glucocorticoids, tiotropium was compared to doubling the dose of glucocorticoids, and was also compared to the addition of salmeterol, a long-acting beta agonist (LABA). Tiotropium was superior to doubling the dose of inhaled glucocorticoid as assessed by measuring the morning peak expiratory flow (PEF) ($P < 0.001$). It also improved evening PEF, asthma control days, and FEV1, as well as daily symptom scores. The addition of tiotropium was also noninferior to the addition of salmeterol for all assessed outcomes and was superior to salmeterol in measures of prebronchodilator FEV1 ($P = 0.003$).

The authors conclude that tiotropium is superior to doubling the dose of glucocorticoid in patients with inadequately controlled asthma, and is equivalent to the addition of salmeterol in the same patient group (published online *N Engl J Med* Sept. 19, 2010). This study is important because it may result in options for patients with poorly controlled asthma beyond adding a LABA. Recently, asthma experts and the FDA have questioned the safety of LABA therapy (FDA Drug Safety Communication June 2, 2010), and a recent meta-analysis suggests that use of LABAs without concomitant inhaled corticosteroids increase the risk for intubation or death (*Am J Med* 2010;123:322-328). ■

Sibutramine pulled from market

Abbott Laboratories announced in October that it is withdrawing the weight-loss drug sibutramine (Meridia®) from the market. The move comes a month after the FDA finished a review of the drug and found that patients with cardiovascular disease or diabetes given sibutramine had a significantly higher rate of serious cardiovascular events compared to placebo. The drug was originally approved in 1997. In a news release, the FDA states "physicians are advised to stop prescribing Meridia to their patients and patients should stop taking this medication." *The Wall Street Journal* reports that while Meridia may be off the market, sibutramine is still available illegally in many weight-loss nutritional supplements, most of which are available via the Internet from oversee suppliers. The supplements are marketed as "all-natural" and their labels list only herbal ingredients. The FDA recently advised consumers that Slimming Beauty Bitter Orange Slimming Capsules contains sibutramine, and last year published a list of more than 50 other supplements containing the banned drug. For complete list of supplements containing sibutramine go to: www.fda.gov/Drugs/ResourcesForYou/Consumers/QuestionsAnswers/ucm136187.htm. ■

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Incidence and mortality data from WHI

In 2002, the Women's Health Initiative (WHI) study was stopped early after 5.6 years when data showed that combination estrogen and progesterone therapy increased the risk of breast cancer. Mortality data had never been reported from WHI, however, and other studies have suggested that hormone therapy-associated breast cancers might have a more favorable prognosis than other breast cancers. A new analysis of WHI data dispels that notion.

The current study is a follow-up study of more than 16,000 women enrolled in WHI who were randomized to conjugated equine estrogen 0.65 mg per day plus medroxyprogesterone 2.5 mg per day (Prempro®) or placebo. Participants were followed for an average of 11 years with the main outcome measure being breast cancer incidence and breast cancer mortality. Women on hormone therapy had a higher rate of breast cancer compared to women on placebo (0.42% vs 0.34% per year; hazard ratio [HR], 1.25; 95% confidence interval [CI], 1.07-1.46; $P = 0.004$) and breast cancers in the hormone group were more likely to be node-positive (23.7% vs 16.2%; HR, 1.78; 95% CI, 1.23-2.58; $P = 0.03$). The death rate associated with breast cancer was higher in the hormone group (0.03% vs 0.01% per year; HR, 1.96; 95% CI, 1.00-4.04; $P = 0.049$), a finding that barely reached statistical significance because of the low number of cancers in either group.

The authors conclude that estrogen plus progesterone was associated with a higher breast cancer incidence, as well as cancers that were more commonly node-positive. Breast cancer mortality was also higher in the combined hormone group (*JAMA* 2010;304:1684-1692). An accompanying editorial points out that despite the borderline statistical significance of these findings it is likely that "the increase in breast cancer deaths due to hormone therapy has been underestimated in the current study." However, it is still unclear whether short courses of hormone therapy for relief of postmenopausal symptoms right after menopause may be safe and further research is needed "to determine whether lower doses or shorter durations of hormone therapy could alleviate menopausal symptoms without increasing cancer risk" (*JAMA* 2010;304:1719-1720). ■

FDA actions

The FDA has approved fingolimod, the first oral drug for the treatment of relapsing forms of multiple sclerosis. Fingolimod is a sphingosine 1-phosphate receptor modulator that is believed to reduce migration of lymphocytes into the central nervous system. Compared to interferon beta-1a, the annualized relapse rate was significantly lower with fingolimod. Patients need to be monitored for decreased heart rate and elevation of liver transaminases. Fingolimod is given as a once-daily 0.5 mg tablet. It is marketed by Novartis as Gilenya™.

As anticipated, the **FDA has approved dabigatran to prevent strokes and blood clots in patients with atrial fibrillation.** The drug is a direct thrombin inhibitor and is given orally twice a day. The approval was based on the RE-LY trial, which showed that dabigatran at 150 mg given twice a day was superior to warfarin for this indication. Unlike warfarin, dabigatran requires no monitoring. Dabigatran will be available in 75 mg and 150 mg capsules and will be marketed as Pradaxa® by Boehringer Ingelheim Pharmaceuticals.

The FDA has ordered a labeling change for bisphosphonates, warning of the risk of atypical femoral fractures. In March, the FDA announced an ongoing safety review of bisphosphonates and the occurrence of subtrochanteric and diaphyseal femoral fractures. The new warning is a result of that review and, while not acknowledging a direct link, the warning suggests that these fractures may be related to use of bisphosphonates for longer than 5 years. The agency further suggests that health care professionals consider periodic reevaluation of the need for continued bisphosphonate therapy in patients who have been on the drugs for more than 5 years. The labeling change will only affect bisphosphonates approved for osteoporosis, which include alendronate (Fosamax®), risedronate (Actonel®), ibandronate (Boniva®), and zoledronic acid (Reclast®).

The FDA has approved extended-release naltrexone to treat and prevent relapse of patients with opioid dependence who have undergone detoxification treatment. Extended-release naltrexone is administered by intramuscular injection once a month, and blocks opioid receptors in the brain. It was initially approved in 2006 to treat alcohol dependence. The drug is only approved for patients who have completed rehabilitation, otherwise it may trigger opioid withdrawal. The efficacy of naltrexone was shown in a 6-month placebo-controlled trial in which treated patients were more likely to stay in treatment and refrain from using illicit drugs. Extended-release naltrexone injection is marketed as Vivitrol® by Alkermes Inc. ■