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Foodborne Infections—Preliminary 2005 FoodNet Data

ABSTRACT AND COMMENTARY

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

Synopsis: *Preliminary FoodNet surveillance data for 2005 show the incidence of infections caused by Campylobacter, Listeria, Salmonella, Shiga toxin-producing* Escherichia coli *0157, Shigella, and Yersinia have declined, whereas Vibrio infections have increased.*

Source: CDC. Preliminary FoodNet Data on the Incidence of Infection with Pathogens Transmitted Commonly Through Food—10 States, United States, 2005. *MMWR Morb Mortal Wkly Rep*. 2006;55:392-395.

In 1996, the FOODBORNE DISEASES ACTIVE SURVEILLANCE NETWORK (FoodNet) was established as a collaborative effort by the Emerging Infections Program of the CDC, the US Department of Agriculture (USDA), the Food Safety and Inspection Service (FSIS), and the US Food and Drug Administration (FDA). FoodNet now includes 10 state health departments (California, Colorado, Connecticut, Georgia, Maryland, Minnesota, New Mexico, New York, Oregon, and Tennessee) which monitor laboratory-confirmed infections of 7 bacterial organisms (Campylobacter, Listeria, Salmonella, Shiga toxin-producing *Escherichia coli* 0157 (STEC 0157), Shigella, Vibrio, and Yersinia) and 2 parasitic (Cryptosporidium and Cyclospora) infections. Since 2000, FoodNet is also collecting data on Shiga toxin-producing *Escherichia coli* non-0157 (STEC non-0157) and hemolytic uremic syndrome (HUS). The surveillance population of FoodNet is now 44.5 million (15% of the US population), and new data for 2005 can be compared with baseline FoodNet data from the period 1996-1998 to examine trends in the incidence of foodborne infections.

A total of 16,614 laboratory-confirmed foodborne illness cases were identified in FoodNet surveillance areas. Salmonella cases were most frequent (6471 cases), with the most common serotypes being Typhimurium (19%), Enteritidis (18%), Newport (10%), Heidelberg (6%), and Javiana (5%). Cases of Campylobacter (5655), Shigella (2078), and Cryptosporidium (1313) followed in frequency. STEC 0157 accounted for 473 cases, an estimated decrease of 29% compared to FoodNet data from 1996-1998. Most of the decline in STEC 0157 incidence occurred during 2003 and 2004. Yersinia (159 cases), STEC non-0157 (146 cases), Listeria (135 cases), Vibrio (119 cases), and Cyclospora (65 cases) made up the remainder of cases.

Compared with the 1996-1998 FoodNet baseline period, the estimated incidence of Campylobacter, Listeria, Salmonella, Shigella, STEC 0157, and Yersinia all declined significantly. Food safety initiatives may have contributed to these declines. The estimated incidence of Vibrio infections increased by 41% compared to baseline, indicating additional efforts are needed to prevent Vibrio infections. Consumption of raw or undercooked oysters is a risk factor for acquisition of Vibrio infections.

COMMENTARY

It is estimated that foodborne diseases secondary to known pathogens cause 14 million illnesses, 60,000 hospitalizations, and 1800 deaths in the United States each year.[1] Foodborne illness often begins with an acute onset of nausea, vomiting, diarrhea, or other gastrointestinal problems. The illness can be self-limited but severe illness, bacteremia, and death are more likely to occur in the very young, elderly, or patients with compromised immune systems. In the United States, older patients represent an increasing proportion of the population. Associated chronic diseases, lower nutritional status, loss of mobility, overuse of H-2 receptor antagonists (hypochlohydria may reduce the ability to resist infection), and improper food preparation and handling can all contribute to the increased risk and severity of foodborne infections in older adults.[2] The risk for foodborne illness can be reduced by avoiding consumption of unpasteurized milk or milk products and raw or undercooked food products, especially eggs, oysters, poultry, or ground beef.

The FoodNet data represent only culture-confirmed laboratory cases of foodborne illness. Many patients may not seek medical attention during foodborne illness and, even if seen by a physician, appropriate stool studies are not always ordered. The Infectious Disease Society of America (IDSA) practice guidelines for infectious diarrhea address this issue by recommending that any patient with community-acquired diarrhea lasting greater than 1 day, especially if accompanied by fever, dehydration, bloody stools, systemic illness, recent antibiotic use, day care center attendance, or hospitalization should have appropriate stool studies.[3] The presence of bloody diarrhea should prompt evaluation for Shiga toxin production if the laboratory has that capability. Ideally, isolates that are positive for Shiga toxin should then be sent to a state public health laboratory for confirmation and STEC serotying. Most laboratories do not have the ability to identify noroviruses, an increasingly recognized cause of foodborne illness. In the future, 2 of the FoodNet laboratories will be implementing a new diagnostic panel for acute diarrheal episodes of unknown etiology, and this information may lead to the identification of new foodborne pathogens.[4]

After *E. coli* 0157 outbreaks associated with ground beef occurred in 1996, the Pathogen Reduction/Hazard Analysis Critical Control Points (HACCP) system of regulation was established. This resulted in the implementation of sampling and microbiologic testing for Salmonella in meat instead of only visual inspection of carcasses. These measures likely contributed to the documented decline in bacterial pathogens since 1996-1998

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noted in the FoodNet data. Of note, the rise in FoodNet Vibrio infections was not related to Hurricane Katrina since the Vibrio cases seen in the aftermath of the hurricane were mostly wound infections (24 cases), with only 4 reported cases of Vibrio gastrointestinal disease.[5]

Two outbreaks of multi-drug resistant (MDR) Salmonella in ground beef occurred in 2003-2004, heightening the concern about the need for surveillance of MDR outbreaks, as well as the development of control strategies. These strategies include improving mechanisms for trace-back investigations, designation of MDR Salmonella as an adulterant in ground beef, and restricting the use of antimicrobial agents in food animals.[5] Restriction of antimicrobial use in food animals is receiving increasing support from consumer groups and public health officials. The WHO has advocated emphasis on restricting the use of critically important antibiotics for human medicine, such as fluoroquinolones, carbapenems, and third generation cephalosporins.[6] A favorable trend toward decreasing the amount of drug-resistant bacteria (ie, vancomycin-resistant enterococci) was noted after the European Union put into place a ban on the use of 4 antibiotics for growth promotion in their food animals.[7] Implementation of similar measures in the United States and other countries would likely make a significant contribution toward reducing future problems with foodborne resistant bacteria. ■

References

1. Mead PS, et al. Food-Related Illness and Death in the United States. *Emerg Infect Dis*. 1999;5:607-625.
2. Kendall PA. Food Safety Guidance for Older Adults. *Clin Infect Dis*. 2006;42:1298-1304.
3. Guerrant RL, et al. Practice Guidelines for the Management of Infectious Diarrhea. *Clin Infect Dis*. 2001;32:331-351.
4. Allos BM, et al. Surveillance for Sporadic Foodborne Disease in the 21st Century: The FoodNet Perspective. *Clin Infect Dis*. 2004;38:S115-S120.
5. Heilpern KL, Borg K. Update on Emerging Infections: News from the Centers for Disease Control and Prevention. Vibrio Illness after Hurricane Katrina—Multiple States, August-September 2005. *Ann Emerg Med*. 2006;47:255-258.
6. Talbot EA, et al. Common Ground for the Control of Multidrug-Resistant Salmonella in Ground Beef. *Clin Infect Dis*. 2006;42:1455-1462.
7. World Health Organization (WHO). Critically Important Antibacterial Agents for Human Medicine for Risk Management Strategies of Non-human Use: Report of a WHO Working Group Consultation, Canberra, Australia, 15-18 February 2005. www.who.int/foodborne_disease/resistance/en Accessed 11 May 2006.
8. Aarestrup FM, et al. Effect of Abolishment of the Use of Antimicrobial Agents for Growth Promotion on Occurrence of Antimicrobial Resistance in Fecal Enterococci from Food Animals in Denmark. *Antimicrob Agents Chemother*. 2001;45:2054-2059.

Endocarditis After Acute Q Fever

ABSTRACT & COMMENTARY

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Synopsis: *Acute Q fever may progress to endocarditis in patients with clinically silent valvulopathy. Those at risk require either extended antibiotic prophylaxis or close serological follow-up. All patients with acute Q fever should undergo transthoracic echocardiography, or in some instances transesophageal echocardiography, to exclude occult valvular abnormalities.*

Source: Fenollar F, et al. Endocarditis After Acute Q Fever in Patients with Previously Undiagnosed Valvulopathies. *Clin Infect Dis*. 2006;42:818-821.

FENOLLAR AND COLLEAGUES REPORT 3 CASES OF *Coxiella burnetii* (Q fever) endocarditis which occurred in patients with previously undetected, clinically silent cardiac valvular abnormalities, months to years after documented acute Q fever. These subtle valvulopathies included bicuspid aortic valve, mitral valve prolapse, and minimal valvular leaks.[1]

Patient 1: A 45-year-old male physician was diagnosed with acute Q fever in May 1998, having presented with acute hepatitis and a positive serological test. He had no detected cardiac murmur. He received doxycycline 200 mg daily for 3 weeks and remained healthy until November 2003, when he experienced dyspnea without fever. The murmur of aortic insufficiency was appreciated on ausculta-

tion. Transesophageal echocardiography (TEE) confirmed aortic insufficiency and revealed a bicuspid aortic valve. Standard blood cultures were negative. *Coxiella burnetii* serology revealed anti-phase I antibodies characteristic of chronic Q fever. The severity of his aortic insufficiency was such that he required valvular replacement. *C. burnetii* was identified by immunohistochemical staining of the valve specimen; PCR and cultures of this specimen were also positive. He received doxycycline (200 mg/day) and hydroxychloroquine (600 mg per day) and remains well.

Patient 2: A 53-year-old woman presented in July 2003, with hepatitis and Q fever serologies characteristic of acute infection (elevated anti-phase II antibodies). She had no significant medical history; no heart murmur was noted. She received doxycycline 200 mg daily for 3 weeks. Two months later, during September 2003, she presented with fever. Mitral valve prolapse, associated with mitral valve vegetations, was found on TEE. Q fever serology was then characteristic of chronic Q fever, with the presence of anti-phase I IgM antibodies. Standard blood cultures remained negative; however, serum PCR was positive for *C. burnetii*. She also received a regimen of oral doxycycline and hydroxychloroquine and is doing well.

Patient 3: A 50-year-old man was diagnosed with acute Q fever in July 2004, having presented with both hepatitis and serum anti-phase II *C. burnetii* IgM titer of 1:1600. He also was treated with doxycycline 200 mg daily for 3 weeks. Medical history and physical exam were unremarkable. A transthoracic echocardiogram (TTE) was completely normal. Six months later, in February 2005, he presented with fever. Transesophageal echo revealed a mitral valve vegetation but only trivial mitral regurgitation. *C. burnetii* serology had evolved to anti-phase I antibodies. He, too, was begun on a regimen of doxycycline and hydroxychloroquine and has remained well.

Fenollar and colleagues conclude that when acute Q fever is diagnosed, it is essential to diagnose any concurrent cardiac valvulopathy, no matter how subtle. With this in mind, all such patients should be subjected to at least transthoracic echocardiography. Those at especially high risk should have transesophageal echocardiography because it affords more sensitive and accurate valvular visualization. Among these are those individuals > 60 years in age and those with a family history of either aortic valve disease or bicuspid aortic valve. Those individuals with abnormal valves should receive either specific long-term antibiotic prophylaxis against the evolution of Q fever or follow-up serology every 3 months, for at least 2 years. A combination of doxycycline (200 mg per day) plus hydroxychloroquine (600 mg per day) administered for 12 months has been suggested as the prophylactic regimen.

COMMENTARY

Q fever represents a nearly worldwide zoonosis caused by the Gram negative, obligate intracellular coccobacillus, *Coxiella burnetii*. Transmission is largely by aerosol; inhalation of virtually a single bacterium may lead to infection. Indeed, *C. burnetii* is listed by the CDC as a Category B bioterrorism agent in part because of this efficiency of transmission.[2] The most common mode of transmission is through inhalation of aerosols originating from the infected products of conception of goats, sheep, cats, and cattle at the time of birth or miscarriage. Cases have also occurred from exposure to hay, straw, dust, and wool that had been in contact with infected animals. Exposure by aerosol has been documented as far as 18 kilometers from the infected source. There is occasional blood-borne and, rarely, person-to-person transmission; consumption of unpasteurized cheese has also been linked to Q fever.[3]

At least 50% of acute Q fever cases are completely asymptomatic, manifesting themselves solely by seroconversion. The most common clinical syndromes are: a flu-like illness with fever, headache, myalgias, pneumonia, and hepatitis.[4] The current recommended therapy is oral doxycycline 200 mg daily for 3 weeks. Although most patients recover completely from Q fever, even without treatment, 1% will go on to develop chronic disease. The majority of these patients will have endocarditis. However, other endovascular infections, osteomyelitis, or joint infections are also possible. Host factors that predispose to these sequelae are pre-existing cardiac and vascular abnormalities, prosthetic valves, grafts, or joint prostheses, and immunosuppressive illnesses such as coexistent malignancy or HIV. Acute Q fever would be expected to result in endocarditis in one-third of individuals with underlying valvular disease.[5]

The transformation from acute to chronic Q fever can be diagnosed by observing the evolution of Q fever serology. Acute infection is characterized by antibodies directed against phase II antigens on the organism. On the other hand, chronic Q fever is diagnosed by detection of antibodies directed against phase I antigens. A titer of antiphase I IgG antibody of > 1:800 and an IgA titer of > 1:100 are diagnostic of chronic Q fever.[6]

Endocarditis is a serious, indeed life-threatening illness, which if untreated may mandate cardiac surgery as for patient one. It is estimated that risk for the development of endocarditis in patients with known valvulopathy and acute Q fever is about 39%. In a previous publication, Fenollar et al proposed that patients with acute Q fever and known cardiovascular defects be treated with combination doxycycline/hydroxychloroquine therapy for one year and followed every 3 months for at least 2 years.[7]

In the more recent article summarized above, Fenollar et al describes 3 patients with normal cardiac findings on physical exam, including one with a normal transthoracic echo who went on to develop chronic Q fever endocarditis. The underlying valvulopathies, later discovered by transesophageal echocardiography,[8] included mitral valve prolapse, minimal valvular leak, and bicuspid aortic valve. Had underlying pathology been detected earlier, antibiotic prophylaxis and/or close follow-up would have prevented clinical disease.

Conversely, Q fever must be considered a possible etiology of culture-negative endocarditis, accounting for about 5% of these cases. We present a patient from the Miriam Hospital, Providence, RI, in whom Q fever developed in the setting of hypertrophic cardiomyopathy. We know of no other similar case report, but we feel this illustrates the range of underlying pathology which must be considered as predispositions to this disease.

Our patient: A 40-year-old woman with hypertrophic cardiomyopathy, diagnosed at age 20, worked in Kingston, Jamaica from 1993 to 1995, where she taught impoverished children living in improvised housing. She had extensive contact with goats and unpasteurized goats' milk. Although she had no documented history of Q fever, in 1996, she had a documented episode of aseptic meningitis. Q fever serologic testing was not performed at that time. In September 2000, she developed fatigue, complete heart block, fever to 102° F, and drenching sweats. Although TTE was similar to a previous study done in March 2000, TEE was remarkable for new mitral valve findings: myxomatous mitral leaflets with a one centimeter, pedunculated mass at the anterior mitral leaflet near the septum, suggesting a vegetation. She also had a thickened aortic valve with severe aortic insufficiency. Several extended blood cultures were negative. *C. burnetii* serum antibody titers were anti- IgG phase I ≥ 1:20148; IgG phase II ≥ 1:2048; IgM phase I 1:64; IgM phase II < 1:16. She has responded over time to extended doxycycline/hydroxychloroquine treatment with size reduction of the vegetation, and no further fever or progression of her aortic insufficiency.

Endocarditis is a serious, not uncommon, yet potentially preventable complication of acute Q fever. Every effort should be made to identify those individuals at risk, including careful, sensitive echocardiography to identify occult cardiac disease. Prolonged antibiotic therapy and/or close serological and clinical observation of these individuals are both reasonable and important strategies to prevent the progression of this disease and the development of life-threatening sequelae. ■

References

1. Fenollar, F, et al. Endocarditis After Acute Q Fever in Patients with Previously Undiagnosed Valvulopathies. *Clin Infect Dis*. 2006;42:818-821.
2. CDC. Emergency Preparedness & Response. www.bt.cdc.gov
3. Raoult D, Marrie T. Q Fever. *Clin Infect Dis*. 1995;20:489-495.
4. Raoult D, et al. Q Fever 1985-1998. Clinical and Epidemiologic Features of 1383 Infections. *Medicine* (Baltimore). 2000;79:109-123.
5. Brouqui P, et al. Chronic Q Fever. Ninety-Two Cases from France, Including 27 Cases Without Endocarditis. *Arch Intern Med*. 1993;153:642-648.
6. Dupont HT, et al. Q Fever Serology: Cutoff Determination for Microimmunofluorescence. *Clin Diagn Lab Immunol*. 1994;1:189-196.
7. Fenollar F, et al. Risks Factors and Prevention of Q Fever Endocarditis. *Clin Infect Dis*. 2001;33:312-316.
8. Jortner R, et al. Transesophageal Echocardiography in the Diagnosis of Q-fever Endocarditis. *Am Heart J*. 1994;128:827-831.

Routine Immunizations for Pediatric Travelers

SPECIAL UPDATE & REPORT

By Philip R. Fischer, MD, DTM&H, and Robert M. Jacobson, MD

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Synopsis: *The schedule of routine vaccinations for children in the United States is modified regularly. Travel medicine practitioners should be aware of current recommendations so that traveling children can benefit from appropriate pre-travel care both during and after their trips.*

Sources: American Academy of Pediatrics Committee on Infectious Diseases. Recommended Childhood and Adolescent Immunization Schedule—United States, 2006. *Pediatrics*. 2006;117:239-240; CDC. Mumps Epidemic—Iowa, 2006. *MMWR Morb Mortal Wkly Rep*. 2006;55:366-368.

With such rapid advances in immunization science and with additional vaccines frequently becoming available, expert groups advising the American

public about immunization practices standardized their recommendations a decade ago. Annually, updates are published by the American Academy of Pediatrics.

This year, several established and emerging innovations are particularly relevant to the care of traveling children. The newly developed meningococcal vaccine should be given to all 11- to 12-year-olds and to all unimmunized individuals entering high school. Hepatitis A is now recommended for all American 1- to 2-year-olds. Adolescents should now be immunized against pertussis as part of their tetanus booster. All children aged 6 to 59 months should receive influenza vaccine.

A recent mumps outbreak has affected hundreds of people in the Midwestern United States. Of 219 Iowa patients evaluated by the CDC, the median patient age was 21 years. At least two-thirds of them had received 2 vaccine doses. With new combination formulations becoming available, mumps vaccination is now urged for unprotected individuals.

New Recommendations

Meningococcus: Meningococcal disease is well-known and respected by travel medicine practitioners. Even in the United States, however, there are approximately 2000 cases of meningococcal disease each year. Despite antibiotic therapy being available, about 10% of affected individuals die of their disease. The new quadrivalent (still just for strains A, C, Y, and W135) is at least as immunogenic to the older vaccine preparations (98-100%), but has a longer duration of protection (8 vs 3-5 years). Despite initial concerns, the risk of Guillain-Barré syndrome does not appear to be increased following use of this vaccine. The new vaccine is preferred for individuals 11-55 years of age. Vaccination is recommended routinely for 11- to 12-year-olds and for older adolescents who did not receive the older (polysaccharide) vaccine during the preceding 5 years.

Hepatitis A: In the late 1990s, 11 US states accounted for 70% of all US cases of hepatitis A. Children were frequently identified as the source of infection that spread to adults. Since 1999, focused vaccination of 2-year-olds in those 11 states has been recommended. As a result, some areas have reported a 90% decrease in cases of adult hepatitis A, and two-thirds of US cases now occur among the remaining unvaccinated persons in 39 states. Between 12 and 24 months of age, 96% of vaccine recipients convert to seropositivity after the first dose of vaccine, and all recipients are found to be seropositive following their second dose, 6 or more months later. The 2 major hepatitis A vaccines, recommended for younger infants in other countries for years, are now licensed for use in 1-year-olds in the United States. It is now recommended that all 1-year-olds be vaccinated against hepatitis A, and that vaccination be considered for older children who were not previously vaccinated. Of course, all children traveling to endemic countries would be candidates for vaccination.

Pertussis: Pertussis vaccination for health care workers was reviewed in last month's *Travel Medicine Advisor*. While infection is most severe, and even potentially fatal during infancy, adolescents and adults in whom vaccine-induced immunity has generally waned, serve as the common source of infection for infants. New combination vaccines include reduced antigen loads, and are both effective and tolerably safe. These new Tdap vaccines are recommended for adolescents who have not yet received their tetanus-diphtheria booster, and the Tdap vaccine is encouraged for adolescents and adults who are in contact with young children and who received the Td booster at least 2-5 years earlier.

Influenza: Vaccination against influenza has been recommended for high-risk individuals. Previously, routine vaccination of children was focused on reducing influenza-related hospitalizations and deaths by targeting children 6-23 months of age. Now, to reduce episodes of illness and outpatient visits as well, vaccination is recommended for all children aged 6-59 months and for those older children and adults who live with or care for pre-school-aged children.

Rotavirus: Worldwide, rotavirus diarrhea kills half a million children each year. In the United States, 2,700,000 children are infected by rotavirus each year, with a cost to the American public of nearly $1 billion. The previously licensed rotavirus vaccine was removed from the market when post-licensure surveillance identified an increased risk of intussusception. Now, a new vaccine has been licensed. The new vaccine is not rhesus-derived and shows less intestinal virus replication. In over 70,000 studied children, no increased risk of intussusception was identified. Nonetheless, there is concern that late administration of older children could pose a risk of intussusception. The new recommendation is that all infants receive rotavirus vaccine at 2, 4, and 6 months of age, with the first dose given no later than 12 weeks of age and the final dose no later than 32 weeks of age. Travel medicine practitioners should ensure that traveling infants in this age group have been vaccinated, but they should not risk use of the vaccine beyond these ages.

Live Vaccines in Infants

The recent fading outbreak of mumps in the midwestern United States has heightened awareness of the importance of obtaining adequate protection using current live virus vaccines. A single dose of the combination measles-mumps-rubella vaccine given at 1 year of age (when competing maternally-derived antibody titers would have

waned) is 80-90% protective against these 3 infections. A second dose is routinely given after infancy, but prior to school entry, and results in 90-95% protection against the 3 infections. As illustrated in the Iowa outbreak, however, compliance with recommended vaccine programs does not insure complete protection. During an active outbreak of measles, mumps, or rubella, or when a child will be traveling, the second dose may be given as early as 4 weeks after the first dose. In an effort to reduce the number of injections a young child receives, a new combination vaccine that also includes varicella vaccine is now recommended for routine use as the first dose in children aged 12 months to 12 years.

What should be done for infants traveling to areas endemic for yellow fever? Fourteen of the 18 cases of vaccine-associated neurotrophic disease have been in infants less than 4 months of age.[2] To decrease the risk of this severe reaction, yellow fever vaccine is considered contraindicated for children less than 6 months of age. Use of yellow fever vaccine in children 6-9 months of age should be undertaken very cautiously, if at all, usually in consultation with experts such as those at the CDC (404-498-1600). For infants who must spend time in areas where yellow fever is a risk, insect avoidance measures (clothes, impregnated bed nets, DEET) are vitally important.

Accelerated Vaccination Schedules

The routine schedules for vaccination of American children are intended for children in routine situations. While foreign travel is increasingly common, it is not yet a routine part of infancy. Thus, routine schedules can be adapted to meet the needs of traveling children. In addition to adding travel-associated vaccines, routine vaccine schedules can be accelerated to provide earlier protection for children at increased risk due to potential travel-related exposures.

Hepatitis B vaccine may be given at birth, with the second dose at 1 month of age. The final dose, ensuring maximal protection, could be given at 6 months of age. Diphtheria, tetanus, pertussis, *Haemophilus influenza* type b, and inactivated polio vaccines are safe and effective when given as early as 6 weeks of age, with subsequent doses as early as 6 week intervals. Pneumococcal vaccine is likely effective at this accelerated rate as well, but data are not available to fully document this currently.

Maternally-derived measles antibody titers subside between 6 and 12 months of age. Thus, children traveling to areas where measles, mumps, and/or rubella are common can receive the combined vaccine as early as 6 months of age—with the thought that it would provide protection for those in whom maternal antibodies are no longer protective. Since the vaccine at this time might not remain fully protective, subsequent doses following the routine schedule should also be given. Similarly, hepatitis A vaccine, though not licensed for use prior to 1 year of age, could provide protection in younger infants who do not have maternally-derived antibody. Varicella vaccine has not been tested prior to 12 months of age, so is not routinely recommended in younger infants.

The older polysaccharide meningococcal vaccine is not completely effective during infancy. It may be used as early as 3 months of age if partial protection is desired. For continued protection, a repeat dose would need to be given sooner (after 2-3 years) than in children vaccinated initially after their fourth birthday (after 3-5 years). Pre-travel consultations provide an excellent opportunity to help pediatric travelers catch up with new recommendations for routine vaccination. Careful attention to the age and timing of vaccination can also help ensure that each traveling child is maximally protected against many of the infectious risks they may encounter. ■

References

1. www.cdc.gov/nip/news/pr/pr_rotavirus_feb2006.pdf, Accessed May 5, 2006.
2. www2.ncid.cdc.gov/travel/yb/utils/ybGet.asp?section=children&obj=child-vax.htm. Accessed May 5, 2006.

Refugees with Eosinophilia: Diagnostic Considerations

ABSTRACT & COMMENTARY

By Michele Barry, MD, FACP

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

Synopsis: *Many refugees arriving in the U.S. have persistent eosinophilia diagnosed and often are referred to travelers' clinics for diagnostic work-up. What does one consider in planning such a workup?*

Source: Seybolt LM, et al. Diagnostic Evaluation of Newly Arrived Asymptomatic Refugees with Eosinophilia. *Clin Infect Dis*. 2006;42:363-367.

Seybolt and colleagues performed a retrospective analysis of refugees seen as part of a 2-visit health evaluation at Boston Medical Center from October 1998 through May 2002. Eosinophilia was defined as an absolute eosinophil count of > 450 cells/µL. Demographic data was abstracted along with results of stool examinations for ova

and parasites, and serologic studies for antibodies to *Strongyloides stercoralis*, schistosomal and filarial species. Eosinophilia was present in 12% of asymptomatic, newly-arrived refugees screened. Pathogens were identified in stool samples of 29% of 265 patients. Serologic testing was performed in only 45% of patients but, of these results, schistosoma serology was positive in 22% (15 patients), *S. stercoralis* in 39% (45 patients), and filarial serology in 18 (51%) of 35 patients tested. Most subjects with pathogens identified were children and more than half were male. The most common stool parasite isolated was one not associated with eosinophilia (ie, *Giardia lamblia*), suggesting that serological testing aimed at looking for other sources of eosinophilia should be performed, even if the presence of pathogens in stool samples is documented.

COMMENTARY

Eosinophilia in a refugee population is common and often reflects tissue-invasive helminths rather than the diagnosis of an atopic or allergic skin condition, commonly seen in US populations. Eosinophilia has been assessed in a traveler's population and is a poor marker of parasitic diseases.[1] However, refugees who have had prolonged exposure to helminths and different economic settings have an increased risk of contracting parasitic infections, and so eosinophilia becomes an important diagnostic clue. Seybolt et al have attempted to demonstrate that serologic testing for schistosoma species, filaria species, and strongyloidiasis might be of benefit in diagnosing patients with more severe eosinophilia.

Not all patients in this report received a serologic evaluation, nor do Seybolt et al present follow-up data; thus, no conclusions as to cost-effectiveness of serologic testing or even resolution of eosinophilia can be made. Furthermore, cross-reactivity of antibody testing and persistent presence of antibodies in patients with past infections may have confounded their results.

However, despite these limitations, this paper remains an excellent reminder that not all asymptomatic eosinophilia can be identified by stool examinations for ova and parasites, and serologic testing for *S. stercoralis*, schistosoma and filarial species should be appropriately obtained for patients from regions where these pathogens are endemic. Nutman, in an accompanying editorial, suggests that when cost is an issue for refugee populations such as Southeast Asians in which strongyloidiasis and hookworm are common, single dose ivermectin and/or albendazole treatment may be empirically indicated.[2,3]

References

1. Libman MD, et al. Screening for Schistosomiasis, Filariasis, and Strongyloidiasis Among Expatriates Returning from the Tropics. *Clin Infect Dis*. 1993;17:353-359.
2. Nutman TB. Asymptomatic Peripheral Blood Eosinophilia Redux: Common Parasitic Infections Presenting Frequently in Refugees and Immigrants. *Clin Infect Dis*. 2006;42:368-369.
3. Muennig P, et al. The Cost-Effectiveness of Ivermectin vs Albendazole in the Presumptive Treatment of Strongyloidiasis in Immigrants to the United States. *Epidemiol Infect*. 2004;132:1055-1063.

CME Questions

9. Which of the following is true about foodborne illnesses?

a. Norovirus foodborne outbreaks are easily detected with routine stool studies.
b. The presence of blood in the stool should prompt stool studies for Shiga toxin and STEC 0157.
c. Secondary to developed immunity, older patients are at less risk for serious side effects of foodborne infections.
d. Vibrio infections are decreasing compared to 1996-1998 data.
e. Visual inspection of carcasses is the best way to improve detection of contaminated raw meat and poultry.

10. Which of the following statements about Q fever is *false*?

a. Q fever is caused by a Gram-negative bacterium transmitted efficiently by aerosolization, at times over long distances.
b. Q fever is a potential cause of culture negative endocarditis in patients following both untreated and treated acute Q fever.
c. Q fever is associated with endocarditis in patients who have underlying heart murmurs, not those patients with subtle valvulopathies detected by echocardiography alone.
d. Serological testing for serum antibodies against various phase antigens of *Coxiella burnetii* is useful in diagnosis of Q fever endocarditis.
e. Antibiotic therapy for bacterial endocarditis caused by *Coxiella burnetii* may be prolonged for a year or more.

11. Which one of the following vaccinations is not currently recommended?

a. meningococcal vaccine for 11-year-olds staying in the United States
b. hepatitis A vaccine for 1-year-olds staying in the United States
c. recently developed combined pertussis vaccine for adolescents visiting developing countries
d. yellow fever vaccine for 6-month-olds living in endemic areas
e. influenza vaccine for 3-year-olds visiting Europe during the winter

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

CME Objectives

The objectives of *Travel Medicine Advisor* are:

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

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

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

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.

Gastric Acid Secretion and the Absorption of Thyroxine

The absorption of thyroxine is strongly influenced by stomach acidity, according to new study. Researchers from Italy looked at 248 patients with multinodular goiter who were treated with thyroxine with a goal thyrotropin (TSH) level of 0.05 to 0.20 mU/L. Of these patients, 53 had *Helicobacter pylori* related gastritis and 60 had atrophic gastritis of the stomach. The reference group comprised 135 patients with multinodular goiter and no gastric disorders. The study also included 11 patients who were infected with *H. pylori* during the study and 10 patients who were treated with omeprazole and had no gastroesophageal reflux. Patients with *H. pylori*-related gastritis, atrophic gastritis, or both had a daily requirement of thyroxine that was 22-34% higher than the reference group. In the 11 patients who became infected with age by lower *H. pylori* during the study, thyrotropin levels increased significantly (P = 0 .002), an effect that was nearly reversed with eradication of *H. pylori*. Treatment with omeprazole also increased serum thyrotropin levels (median 1.70mU/L increase in thyrotropin; P = 0.002), requiring a 37% increase in thyroxine dose.

The authors conclude that normal gastric acid secretion is necessary for effective absorption of thyroxine, and factors that impair acid secretion including atrophic gastritis, *H. pylori* gastritis, and treatment with omeprazole require increased doses of thyroxine (*N Engl J Med*. 2006;354:1787-1795). This study has important implications, given millions of patients who take thyroxine, the frequency of *H. pylori* infections in this country, and frequency of use of OTC and prescription proton pump inhibitors.

Can Plavix Add to the Efficacy of Aspirin?

Does clopidogrel (Plavix) add to the efficacy of low aspirin in patients with vascular disease? No, according to new study published in the April 20th *New England Journal of Medicine*. CHARISMA (Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance) is a multinational study which randomized 15,603 patients with either clinically evident cardiovascular disease or multiple risk factors to receive clopidogrel (75 mg/d) plus low-dose aspirin (75-162 mg/d) or placebo plus low-dose aspirin for median of 28 months. The efficacy primary end point was a composite of myocardial infarction, stroke, or death from cardiovascular causes. The rate of this end point was 6.8% with the combined drug treatment versus 7.3% with aspirin plus placebo (P = 0.22) for the subgroup of patients with multiple risk factors, the rate of the primary end point was lower for aspirin plus placebo (5.5% aspirin plus placebo versus 6.6% aspirin plus clopidogrel; P = 0.20) and the rate of death from cardiovascular causes was also higher with clopidogrel plus aspirin vs aspirin plus placebo (3.9% versus 2.2%; P = 0.01).

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In the subgroup with clinically evident atherothrombosis, there was a slight benefit for aspirin plus clopidogrel (6.9% versus 7.9%, P = 0.46).

The authors conclude that overall, clopidogrel plus aspirin was not significantly more effective than aspirin alone in reducing the rate of myocardial infarction, stroke, or death from cardiovascular disease (*N Engl J Med*. 2006;354:1706-1717). An accompanying editorial acknowledges that there were many subgroups within CHARISMA that showed varying outcomes with clopidogrel plus aspirin, but cautions against differentiating patients along the lines used in the study. The editorialists find that "these data showed no significant benefit associated with long-term clopidogrel therapy in addition to aspirin." (*N Engl J Med*. 2006;354:1744-1746).

Prevention of Hypertension?

Prehypertension is defined as blood pressure in the range of 120 to 139 mm Hg systolic or 80 to 89 mm Hg diastolic. Since JNC-VII, there has been increased interest in prehypertension since it has been associated with excess morbidity and deaths from cardiovascular causes. A new study suggests that pharmacologic intervention in patients with prehypertension may help prevent progression to hypertension. The Trial of Preventing Hypertension (TROPHY) looked at 809 patients with prehypertension. A total of 409 patients were randomly assigned to candesartan or placebo for 2 years, followed by 2 years of placebo for both groups. When a study participant reached the study end point of stage I hypertension, they were treated with antihypertensive agents.

Both treatment and placebo groups were instructed in lifestyle changes to reduce blood pressure throughout the trial. During the first 2 years, hypertension developed in 154 participants in the placebo group and 53 in a candesartan group ($P < 0.001$). After 4 years, hypertension had developed in 240 participants in the placebo group and 208 in the candesartan group (relative risk reduction 15.6%; $P < 0.007$). Serious adverse events were slightly higher in the placebo group.

The authors conclude that treatment of prehypertension with candesartan was well-tolerated and reduced the risk of incident hypertension during the study period (*N Engl J Med*. 2006;354:1685-1697). In an accompanying editorial, it is pointed out the prehypertension is present in the about 70 million Americans, and is estimated to decrease average life expectancy by as much as 5 years. Despite this, the author urges caution in recommending wholesale treatment of all patients with prehypertension until more information is available on which drugs are most effective and the best duration of therapy. In the meantime, lifestyle changes, which benefit all risk factors, should be recommended for all patients with prehypertension (*N Engl J Med*. 2006;354:1742-1744).

Estrogen Alternatives

Since publication of the Women's Health Initiative (WHI), many postmenopausal women have discontinued estrogen, and most newly menopausal women are considering alternatives. A recently published paper systematically reviews clinical trials of nonhormonal treatments for hot flashes. More than 4000 studies were considered. Forty-three trials met inclusion criteria, including 10 trials of antidepressants, 10 trials of clonidine, 6 trials of other medications, and 17 trials of isoflavone extracts. In the antidepressant group, both selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs) were effective in decreasing the daily number of hot flashes compared to placebo (mean difference -1.13; 95% CI, -1.70 to -0.57). Clonidine was also somewhat effective (-0.95; 95% CI, -1.44 to - 0.47), as was gabapentin (-2.05; 95% CI, -2.80 to -1.30). Red clover isoflavone extracts were not effective, and mixed soy isoflavones had mixed results. The authors conclude that SSRIs, SNRIs, clonidine, and gabapentin provide evidence for some efficacy; however, none are as effective as estrogen (*JAMA*. 2006;295:2057-2071).

FDA Actions

In April, the FDA issued a statement rejecting the medical use of marijuana, citing past evaluations by several US government agencies that showed that "no animal or human data supported the safety or efficacy of marijuana for general medical use." The statement supports the Drug Enforcement Agency's approach to treating all use of marijuana as a criminal act.

Zanamivir (Relenza), GlaxoSmithKline's inhaled anti-influenza drug has received a new indication for prophylaxis of influenza in patients age 5 years and older. The approval was based on 4 large-scale, placebo-controlled trials which showed that the drug was effective in reducing spread of influenza among household members and in community outbreaks. ■