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Infectious Disease [ALERT]

A monthly update of developments in infectious disease, hospital epidemiology, microbiology, infection control, emporiatrics, and HIV treatment

ABSTRACT & COMMENTARY

European measles outbreaks continue: Past gains lost to vaccine objections

By Stan Deresinski, MD, FACP, FIDSA

Clinical Professor of Medicine, Stanford University, Associate Chief of Infectious Diseases, Santa Clara Valley Medical Center, is Editor for Infectious Disease Alert.

SOURCE: Centers for Disease Control and Prevention (CDC). Increased transmission and outbreaks of measles - European region, 2011. *MMWR Morb Mortal Wkly Rep* 2011:60:1605-1610.

The importation of measles into the U.S. was discussed in these pages earlier this year[1]. Europe was the source of a number of cases and it was pointed out that between 2005 and 2008, almost 2 of 5 imported cases were the result of exposure to the virus in that region of the world. The significant progress toward the World Health Organization goal of elimination of measles in the European zone that had been made during 2003-2008 has, unfortunately, been reversed and increased transmissions, often in outbreak settings, have become widespread. A total of 115 outbreaks were reported by 36 of 53 European Region member states so far in 2011. As of October 26, a total of 26,074 cases of measles had been reported, with France accounting for more than half. One-fourth of cases occurred in children <5 years of age, another fourth in those 5-14 years, and one-half in those >15

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years of age. The vaccination status was unknown for 45.4% while 45.1% were known to not have been vaccinated. Nine measles-associated deaths were reported, including 6 in France, where national coverage with a single dose of a measles-containing vaccine was only 87%-90% during 2004-2010. This vaccination rate may be compared to the 90%-92% coverage of the region as a whole. Unfortunately vaccination rates <95% can support continuing transmission and lead to large outbreaks such as those being experienced in the European zone.

■ COMMENTARY

The settings in which transmission occurred included, in addition to the general community, groups with religious or philosophical objections to vaccination, underserved populations with limited healthcare access, health-care facilities, and schools. Within specific countries, outbreak settings also included vacation camps in France and rural populations in Romania. Fourteen cases of measles in healthcare providers at public hospitals in Marseilles, France, were identified between April and November 2010 with 12 of the cases believed to have been acquired in the hospital setting[2]. Six of the providers had never been vaccinated and 4 had received only a single dose of vaccine during childhood.

The reasons for the inadequate vaccination rates in the European zone include lack of knowledge regarding the seriousness of measles infection, public skepticism about the benefits and safety of vaccines, and, in some cases, limited access to healthcare. A growing problem, particularly in western Europe, is that of religious and philosophical objections to vaccination. While Europe is the source of a large proportion of measles cases imported into the U.S., other countries also pose a risk. Within Africa, Nigeria and Somalia have each had >15,000 cases in the last year and Congo has had >100,000. It is clearly important that, in addition to adhering to current recommendations for measles vaccination for the general population, attention be focused on measles associated with international travel. Thus, U.S. residents traveling abroad should be fully vaccinated. While children ordinarily receive their first dose of MMR or MMRV at 12 months of age, MMR should be administered to children as young as 6 months who are traveling internationally. Mass gatherings provide a significant risk for large outbreaks. For instance, The UEFA European Football Championship tournament begin 8 June 2012 in Poland and Ukraine with the championship game on July 1. The 2008 series, held in Austria and Switzerland, drew an average attendance of 38,803 per match and a total attendance of 1,140,902. The potential for outbreaks is obvious.

Finally, clinicians must remain alert to the manifestations of measles in order to rapidly diagnose cases and thus reduce the risk of further transmissions. ■

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ABSTRACT & COMMENTARY

Cytomegalovirus Persists on Surfaces, Posing Risk during Pregnancy

By Hal B. Jenson, MD, FAAP

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Dr. Jenson reports no financial relationship in this field of study.

SYNOPSIS: Cytomegalovirus (CMV) applied to various surfaces was found to be viable on rubber, cloth, and wheat cracker up to 6 hours, glass and plastic up to 3 hours, and metal and sanded wood up to 1 hour. CMV viability was shorter on poorly absorbent surfaces compared to absorbent surfaces.

SOURCE: Stowell JD, Forlin-Passoni D, Din E, et al: Cytomegalovirus survival on common environmental surfaces: Opportunities for viral transmission. *J Infect Dis* 2011 Nov 23. [Epub ahead of print]

Seven types of common environmental surfaces—rubber, glass, plastic, metal, sanded wood, cloth, and wheat crackers—were studied for recovery of ~200 viable virions of CMV strain AD 169 applied to 2 cm2 replicates on each surface. Virus was applied in 200 µL aliquots of phosphate-buffered saline (PBS). At time points from 1 minute to 6 hours an additional 100 µL aliquot of PBS was used to rewet the surface and collect the sample. For cloth and cracker, the entire 2 cm2 sample area was collected and centrifuged to collect the liquid. A 100 µL aliquot of the collection was cultured for CMV for ≥2 weeks using standard methods and scored from 0 to 4+ based on the extent of cytopathic effect. The remaining collection was tested for CMV by quantitative real-time polymerase chain reaction (PCR).

The quantity of infectious virions declined over time for each surface. The duration of CMV viability was generally shorter on poorly absorbent surfaces compared with absorbent surfaces. Of the poorly absorbent surfaces, CMV viability was longest on rubber with persistence for up to 6 hours, with persistence of 3 hours on glass and plastic, 2 hours on metal, and <2 hours on sanded wood. CMV viability was 6 hours on both cloth and wheat crackers with cloth showing greatest viral viability with 4+ cytopathic effect at 3 hours after application. The cracker surface remained visibly moist throughout the 6-hour study period. There was a correlation of reduced viability with the subjective visual observation of the surface becoming dry. Results of PCR showed that CMV DNA was readily detected on all 7 surfaces throughout the 6 hours of study.

■ COMMENTARY

CMV is the most common congenital infection, affecting 1-2% of all live births, and is now recognized as a leading cause of congenital hearing loss and other neurological sequelae. In the United States, approximately 6000 children each year have permanent sensorineural hearing loss and intellectual disability resulting from congenital infection.

Transmission of CMV occurs via direct contact with saliva and urine from infected individuals. Asymptomatic shedding of virus persists from weeks to months after initial infection. Children who are congenitally infected may shed virus for the first several years of life.

These results demonstrate that viable CMV persists up to at least 6 hours on a variety of types of fomites as long as they remain moist. Young children who become infected with CMV shed virus for extended periods, contaminating toys and food in the environment, which poses a risk for pregnant women. To minimize the risk of acquiring CMV during pregnancy, it is usually recommended that pregnant women take precautions to avoid sharing food or fomites with young children, and wash their hands after touching toys and other fomites that have been in contact with children's saliva. This seems reasonable and may be possible for the nulliparous pregnant woman who is not already the caretaker of another young child. However, this guidance seems impractical if not impossible for a pregnant woman who is already the mother

and caretaker of a young child. The continual risk of maternal exposure to CMV, which may not be feasible to mitigate in many cases, underscores the need to develop an effective CMV vaccine to prevent the serious and frequent sequelae of congenital CMV infection. ■

ABSTRACT & COMMENTARY

A Reassurring Analysis on the Safety of Efavirenz in Pregnancy

By Dean L. Winslow, MD, FACP, FIDSA

Chief, Division of AIDS Medicine, Santa Clara Valley Medical Center;
Clinical Professor, Stanford University School of Medicine, is Associate Editor for Infectious Disease Alert.

Dr. Winslow is a speaker for Cubist Pharmaceuticals and GSK, and is a consultant for Siemens Diagnostics

SYNOPSIS: A meta-analysis of 21 studies was conducted. In these studies, there were 39 birth defects in 1437 pregnancies where the mother received efavirenz during the first trimester. The relative risk of defects in women who received efavirenz vs. those who received non-efavirenz-based regimens was 0.85.

SOURCE: Ford N, et al. Safety of efavirenz in first-trimester of pregnancy: an updated systematic review and meta-analysis. *AIDS* 2011; 25: (epub ahead of print).

An updated meta-analysis of birth defects in infants with first trimester efavirenz exposure was conducted and included published literature up until July 2011. In 21 studies included in the analysis, 39 defects were observed among 1437 women receiving first trimester efavirenz (2% incidence). 316 defects were reported in 8122 live births among women who received first trimester non-efavirenz-containing regimens (2.9% incidence) yielding a relative risk of 0.85 for women receiving first trimester efavirenz. One neural tube defect (myelomengocele) was observed in an infant born to a woman who received efavirenz in the first trimester (0.07% incidence).

■ COMMENTARY

Concerns about efavirenz-induced fetal effects began after a DuPont teratogenicity trial conducted in cynomolgus monkeys was reported[1]. In this trial, monkeys were exposed to efavirenz at concentrations similar to those expected in humans receiving the standard 600 mg/day dose. No congenital malformations were observed in 20 control animals, but 3 of 20 efavirenz-exposed infants had major abnormalities. These included anencephaly and unilateral anopthalmia in one monkey, micropthalmia in a second animal, and cleft palate in a third infant monkey.

Retrospective reports have described four cases of CNS malformations in human infants with first trimester efavirenz exposure[2]. (Three infants had myelomeningocele and one had Dandy-Walker malformation.) It should be pointed out that retrospective case reports of potential teratogenic effects of drug exposures in humans are difficult to interpret since neural tube defects are among the most commonly-observed birth defects (about 1 in 1,000 pregnancies). In many cases these likely represent "background" occurrences rather than events caused by a particular prenatal exposure.

This thorough meta-analysis by Ford et al is reassuring that congenital malformations are not likely to be caused by efavirenz in humans. While avoiding efavirenz use in HIV-infected women during the first trimester of pregnancy is still prudent, it should allay excessive concern when this exposure inadvertently occurs for a short period of time when a woman becomes pregnant while receiving efavirenz. ■

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2. Chersich MF, et al. Efavirenz use during pregnancy and for women of child-bearing potential. *AIDS Res Ther* 2006; 3:1-6.

Physician Protect Thyself (and Your Patients and Coworkers)!

By Stan Deresinski, MD, FACP, FIDSA

Clinical Professor of Medicine, Stanford University, Associate Chief of Infectious Diseases, Santa Clara Valley Medical Center, is Editor for Infectious Disease Alert.

SOURCE: Centers for Disease Control and Prevention. Immunization of Health-Care Personnel Recommendations of the Advisory Committee on Immunization Practices (ACIP). Recommendations and Reports. *MMWR Morb Mortal Wkly Rep* 2011:60 (RR07);1-45.

The Advisory Committee on Immunization Practices (ACIP) of the CDC has updated their recommendations for immunization of health care providers (HCP) against communicable infectious diseases.[1] These recommendations apply, but are not limited, to HCP in acute-care hospitals, long-term-care facilities (e.g., nursing homes and skilled nursing facilities), physician's offices, rehabilitation centers, urgent care centers, and outpatient clinic,s as well as to persons who provide home health care and emergency medical services. Evidence indicates that HCP are considered to be at substantial potential risk for acquiring or transmitting hepatitis B, influenza, measles, mumps, rubella, pertussis, and varicella and much of the focus of the recommendations deals with these infections.

Vaccines for HCP Because of the Potential of Occupational Exposure of HCP or of Patients.
Recommendations for immunization of HCP were last published by CDC in 1997. The following is a summary of important changes made in the new document. The original document should be consulted for full details.

Hepatitis B Virus (HBV).
HCP and trainees in certain populations at high risk for chronic HBV infection (e.g., those born in countries with high and intermediate endemicity) should be tested for HBsAg and anti-HBc/anti-HBs to determine infection status.

Influenza.
Emphasis is placed on a recommendation that all HCP, not just those involved in direct patient care, should receive an annual influenza vaccination. Institutions should develop comprehensive programs designed to increase vaccine coverage among HCP. Influenza vaccination rates among HCP within facilities should be measured and regularly reported.

Measles, Mumps, Rubella (MMR).
A history of prior infection in the absence of laboratory confirmation is no longer considered adequate presumptive evidence of measles or mumps immunity for HCP. Laboratory confirmation of disease was added as acceptable presumptive evidence of immunity. Of note is that a past history of disease has never been considered adequate evidence of immunity to rubella.
A change has been made in the footnotes regarding recommendations for personnel born before 1957 in both routine and outbreak contexts. Specifically, guidance is provided for 2 doses of MMR for measles and mumps protection and 1 dose of MMR for rubella protection in the absence of written documentation of vaccination adequate vaccination or laboratory evidence of immunity, or birth before 1957.

Pertussis.
HCP, regardless of age, should receive a single dose of Tdap as soon as feasible if they have not previously received Tdap.
The previously recommended minimal interval was removed, and Tdap can now be administered regardless of the interval since the last receipt of tetanus or diphtheria-containing vaccines.
Hospitals and ambulatory-care facilities should provide Tdap for HCP and use approaches that maximize vaccination rates.

Varicella Zoster.
Criteria for evidence of immunity to varicella were established for HCP and they include
Written documentation of receipt of 2 doses of vaccine,
Laboratory evidence of immunity or laboratory confirmation of disease,
A documented diagnosis of a history of varicella disease made by a HCO, or diagnosis of history of herpes zoster by a HCP.

Meningococcus.
HCP with anatomic or functional asplenia or persistent complement component deficiencies should now receive a 2-dose series of meningococcal conjugate vaccine. HCP with HIV infection who are vaccinated should also receive a 2 dose series.

Those HCP who remain in groups at high risk should be revaccinated every 5 years.

Other Vaccines Recommended for Adults, Whether HCP or Not.
Certain vaccines are recommended for adults based on age or other individual risk factors but not because of occupational exposure and should be considered by HCP. Vaccine-specific ACIP recommendations should be consulted for details on schedules, indications, contraindications, and precautions for these vaccines. Thus, the infections prevented are not generally considered to cause significant risk of transmission from patient to HCP nor the reverse.

• **Pneumococcal polysaccharide vaccine (PPSV).** PPSV is recommended for healthy persons aged ≥65 years. PPSV is also recommended for persons aged <65 years with certain underlying medical conditions, including anatomic or functional asplenia, immunocompromise (including HIV infection), chronic lung, heart or kidney disease, and diabetes.

• **Tetanus and diphtheria toxoids (Td).** All adults should have documentation of having received an age-appropriate series of Td-containing vaccine and a routine booster dose every 10 years. Persons without documentation of having received a Td series should receive a 3-dose series. The first dose of the series should be administered as Tdap (see Pertussis above).

• **Human papillomavirus (HPV) vaccine.** Either quadrivalent HPV vaccine (Gardasil) or bivalent HPV vaccine (Cervarix) is recommended for females at age 11 or 12 years with catch-up vaccination recommended through age 26 years. Quadrivalent HPV vaccine (Gardasil) may be administered to males aged 9-26 years.

• **Zoster vaccine.** Zoster vaccine contains the same live attenuated varicella zoster virus as varicella vaccine but at a higher concentration (approximately 14 times more vaccine virus per dose). Zoster vaccine is recommended for the prevention of HZ (shingles) in persons aged ≥60 years. Transmission of vaccine virus from the recipient to a contact has not been reported. Consequently, limiting or restricting work activities for persons who recently received zoster vaccine is not necessary.

Summary of Recommendations
(For complete recommendations, see original publication)

Vaccination	Indications
HBV	Prexposure: HCP at risk for exposure to blood & body fluids; Postexposure for selected individuals
Influenza	All HCP (absent allergy to eggs or vaccine). HCP who care for severely immunosuppressed persons who require a protective environment should receive inactivated rather than live attenuated vaccine
Measles	Recommended for all HCP who lack presumptive evidence of immunity without contraindications including relevant severe allergy, pregnancy & immunocompromise; vaccination should be considered for those born before 1957
Mumps	Recommended for all HCP who lack presumptive evidence of immunity without contraindications including relevant severe allergy, pregnancy & immunocompromise
Rubella	Recommended for all HCP who lack presumptive evidence of immunity without contraindications including relevant severe allergy, pregnancy & immunocompromise
Tetanus, Diphtheria, Pertussis (Tdap)	Recommended for all HCP absent serious allergic reaction (i.e., anaphylaxis) to any component of Tdap
Varicella	Recommended for all HCP who lack presumptive evidence of immunity without contraindications including relevant severe allergy, pregnancy & immunocompromise. Avoid salicylate use for 6 weeks after vaccination.
Quadrivalent Meningococcal	Microbiologists with potential exposure
Typhoid	Microbiologists with potential exposure; no oral vaccine (Ty21a) for immunompromised or those receiving antibiotics
Inactivated Polio	Adults at increased risk of exposure absent allergy to components

SOURCE: Centers for Disease Control and Prevention

• **Hepatitis A vaccine.** HCP have not been demonstrated to be at increased risk for hepatitis A virus infection because of occupational exposure, including persons exposed to sewage. Hepatitis A vaccine is recommended for person with chronic liver disease, international travelers, and certain other groups at increased risk for exposure to hepatitis A.

Catch-Up and Travel Vaccination
Programs should be implemented designed to enhance the safety of HCP and patients by systematically assuring that HCP are up-to-date on all vaccinations and that they receive appropriate preparation before travel to regions in which they may be at increased risk of certain infections.

Catch-Up Programs.
Managers of health-care facilities should implement catch-up vaccination programs for HCP who already are employed, in addition to developing policies for achieving high vaccination coverage among newly hired HCP. HCP vaccination records could be reviewed annually during the influenza vaccination season or concurrent with annual TB testing. This strategy could help prevent outbreaks of vaccine-preventable diseases. Because education, especially when combined with other interventions such as reminder/recall systems and low or no out-of-pocket costs, enhances the success of many vaccination programs, informational materials should be available to assist in answering questions from HCP regarding the diseases, vaccines, and toxoids as well as the program or policy being implemented. Conducting educational workshops or seminars several weeks before the initiation of a catch-up vaccination program might promote acceptance of program goals.

Travel.
Hospital personnel and other HCP who perform research or health-care work in foreign countries might be at increased risk for acquiring certain diseases that can be prevented by vaccines recommended in the United States (e.g., hepatitis B, influenza, MMR, Tdap, poliovirus, varicella, and meningococcal vaccines) and travel-related vaccines (e.g., hepatitis A, Japanese encephalitis, rabies, typhoid, or yellow fever vaccines). Elevated risks for acquiring these diseases might stem from exposure to patients in health-care settings (e.g., poliomyelitis and meningococcal disease) but also might arise from circumstances unrelated to patient care (e.g., in areas of high endemicity of hepatitis A or after exposure to arthropod-vector diseases [e.g., yellow fever]). All HCP should seek the advice of a health-care provider familiar with travel medicine at least 4-6 weeks before travel to ensure that they are up to date on routine vaccinations and that they receive vaccinations recommended for their destination. Although bacille Calmette-Guérin vaccination is not recommended routinely in the United States, HCP should discuss potential beneficial and other consequences of this vaccination with their health-care provider.

Work Restrictions of Susceptible HCP.
Work restrictions for susceptible HCP (i.e., no history of vaccination or documented lack of immunity) exposed to or infected with certain vaccine-preventable diseases can range from restricting individual HCP from patient contact to complete exclusion from duty. A furloughed employee should be considered in the same category as an employee excluded from the facility. ■

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1. Centers for Disease Control and Prevention Immunization of health-care workers: recommendations of the Advisory Committee on Immunization Practices (ACIP) and the Hospital Infection Control Practices Advisory Committee (HICPAC). *MMWR Morb Mortal Wkly Rep* 1997;46(No.RR-18).

ABSTRACT & COMMENTARY

B-lactam/B-lactamase Inhibitors for Treatment of Bacteremia due to ESBL-producing *E.coli*

By Dean L. Winslow, MD, FACP, FIDSA
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Clinical Professor, Stanford University School of Medicine, is Associate Editor for Infectious Disease Alert.
Dr. Winslow is a speaker for Cubist Pharmaceuticals and GSK, and is a consultant for Siemens Diagnostics

SYNOPSIS: A post hoc analysis of patients with bacteremia due to ESBL-producing E.coli (ESBL-EC) from 6 published cohorts was performed. Treatment with B-lactam/B-lactamase inhibitors (BLBI) vs.

carbapenems did not show any difference in mortality or length of hospital stay.

SOURCE: Rodriguez-Bano, J, et al. B-lactam/B-lactamase inhibitor combinations for the treatment of bacteremia due extended-spectrum B-lactamase-producing Escherichia coli: a post hoc analysis of prospective cohorts. *Clin Infect Dis* 2011; epub ahead of print, Nov 4, 2011.

A post hoc analysis was performed on patients with ESBL-EC bloodstream infections from 6 published prospective cohorts. Mortality and length of hospital stay in patients treated with BLBLI (amoxicillin-clavulanic acid or piperacillin-tazobactam) vs. carbapenem were compared in 2 cohorts: empirical therapy (ETC) and definitive therapy (DTC). Multivariate analysis was used to minimize confounding.

ETC included 103 patients (72 BLBLI, 31 carbapenem) and DTC included 174 patients (54 BLBLI, carbapenem 120). In the ETC, day 30 mortality rate was 9.7% for patients treated with BLBI and 19.4% for carbapenems. In the DTC, day 30 mortality rate was 9.3% in BLBI-treated patients and 16.7% for carbapenem-treated patients. After adjustment for confounders, no association between mortality nor hospital length of stay was seen for BLBI vs. carbapenem therapy in either empiric or definitive therapy of bacteremia due ESBL-EC.

■ COMMENTARY

ESBL-producing gram negative bacteria have emerged as a cause of serious infections over the last 30 years. These Ambler Class A B-lactamases are generally identified in vitro by resistance to first, second, many third generation cepalasporins, and often resistance to fourth generation cephalosporins, however they remain susceptible in vitro to BLBLI and carbapenems. Reluctance to use BLBLI to treat ESBL-EC infections is due to the fact that routine in vitro antibacterial susceptibility testing is performed with a fairly low standardized inoculum of 10e5 cfu/mL. It has been shown that the MIC's of ESBL-producing organisms often increase significantly when the inocula reach 10e7 cfu/mL or greater, as would be expected in some infected tissues in vivo. This effect is thought to be due to the overproduction of B-lactamase "overwhelming" the B-lactamase inhibitor. Due to this theoretical concern, it has largely been dogma that BLBLI's should not be used for treatment of life-threatening infections due to ESBL-expressing bacteria, and rather that carbapenems (which are resistant to hydrolysis by ESBL) should be used.

Unfortunately, carbapenem resistance has been increasing dramatically over the past few years and can be due to a variety of mechanisms including hydrolysis by carbapenemases from Ambler classes A, B, and D B-lactamases. The Ambler class B enzyme (metallo-B-lactamase), NDM-1, has now been recognized on most continents and is of great concern. This paper suggests that treatment of ESBL-EC infections with BLBLI may be effective in many circumstances. Certainly the results of this post hoc analysis suggest that BLBLI should be compared to carbapenem therapy of ESBL-expressing bacterial infections in a prospective randomized clinical trial. ■

ABSTRACT & COMMENTARY

Fever in Travelers After Visiting Malaria-endemic Areas

By Lin H. Chen, MD

Dr. Chen is Assistant Clinical Professor, Harvard Medical School;
Director, Travel Medicine Center, Mt. Auburn Hospital, Cambridge, MA

Dr. Chen has received research grants from the Centers for Disease Control and Prevention and Xcellerex.

SYNOPSIS: Common specific causes of fever in Finnish returned travelers were Campylobacter, malaria, bacteremia, HIV, and influenza; they included a significant proportion of potentially life-threatening infections, and more than one diagnosis. Evaluation of such fevers should be systematic and thorough.

SOURCE: Siikamaki HM, Kivela PS, Sipila PN, et al. Fever in travelers returning from malaria-endemic areas: Don't look for malaria only. J Travel Med 2011;18:239-244.

Authors from the helsinki university central hospital, a tertiary hospital in Finland, retrospectively reviewed patient records from 2005 to 2009 to define the causes of fever in returned travelers and to evaluate the diagnostic approach. The 462 records were selected through

requests for malaria smears in the emergency department.

The most common categories of diagnoses were acute diarrhea (27%), systemic febrile illness (21%), and respiratory illness (15%). Campylobacteriosis was the most common specific diagnosis (9%), while malaria was diagnosed in 4%. Bacteremia was identified in 5% of patients tested (21/428), and influenza was diagnosed in 8 patients. HIV antibodies were performed in 174 patients (38%) and 3% were positive. Non-infectious etiologies caused fever in 3%, and in 25% of the cases the etiology remained unknown.

Potentially life-threatening illnesses were diagnosed in 26% of the patients, and were associated with elevated C-reactive protein (CRP) ≥ 100 (odds ratio [OR], 3.6; 95% confidence interval [CI], 2.0-6.4) and thrombocytopenia (OR, 3.8; 95% CI, 2.0-7.3). One patient died of septicemia. Forty-five patients (10%) had more than one diagnosis.

■ COMMENTARY

A number of serious, life-threatening infections can cause fever in a returned traveler, and the evaluation may be challenging for clinicians unfamiliar with the epidemiology at the destination countries. Data from studies on travelers are welcome to further strengthen work-ups for particular diagnoses.

A well-established network of specialized travel and tropical medicine clinics, GeoSentinel, analyzed fever in 24,920 returned travelers seen from March 1997 through March 2006 and found fever to be the main cause for seeking medical evaluation in 6,957 (28%).[1] In that analysis, 15% of the fever cases were due to diarrheal disease, 14% due to respiratory illness, and 35% had a febrile systemic illness. Malaria, found in 21% of febrile returned travelers, was the most common specific cause identified.[1] Etiologies for fever varied by region visited and by time of presentation after travel, and the most significant risk factors were travelers who visited sub-Saharan Africa, south-central Asia, and Latin America and whose reason for travel was visiting friends and relatives (VFR). Malaria caused 33% of the 12 deaths among febrile travelers.[1]

A number of centers have studied fever in their returned travelers. A prospective observational study from January 1997 to December 2001 on fever in returning travelers (n = 147) admitted to a university teaching hospital in Milan, Italy, found that malaria accounted for nearly half of admissions (47.6%), followed by presumed self-limiting viral infections (12%).[2] The most useful investigations at this center were blood smears and PCR for malaria, which were positive in 65% of cases for which they were performed. Serology was useful to identify hepatitis A and dengue virus infections.[2]

Investigators in Marseilles, France, also conducted a 5-year prospective observational study on the etiologies of fever in travelers returning from the tropics admitted to a university teaching hospital (n = 613).[3] Malaria was the most common diagnosis (75.2%), with most cases (62%) acquired by VFR travelers from the Comoros Islands; 8.2% of the patients remained unexplained.[3]

Bottieau et al from University Hospital Antwerp, Belgium, also analyzed the etiology of fever and diagnostic predictors from April 2000 to December 2005 in nearly 2,000 returned travelers.[4,5] Exposures occurred commonly in sub-Saharan Africa and Southeast Asia-Pacific (68% and 12%, respectively).[4] Tropical diseases accounted for 39% of the cases, cosmopolitan infections for 34%, and 24% remained unknown. Approximately one-quarter required hospitalization.

The travel destinations were major determinants of tropical infections, with malaria and rickettsial infections as the leading diagnoses after a stay in Africa (35% and 4%, respectively); dengue, malaria, and enteric fever after travel to Asia (12%, 9%, and 4%, respectively); and dengue and malaria on return from Latin America (8% and 4%, respectively).[4]

Although malaria accounted for only 4% of the diagnoses in the study by Siikamaki et al, other European studies found malaria to be a more significant cause of morbidity,[1-5] and also a major cause of mortality.[1,4] Therefore, malaria remains one of the most important diagnoses to exclude when a returned traveler presents with fever. Some findings associated with malaria from these studies include splenomegaly, thrombocytopenia, lack of localizing symptoms, and hyperbilirubinemia.[5] Other key predictors of fever etiology include: skin rash and skin ulcer for rickettsial infection (mainly African tick bite fever); skin rash, thrombocytopenia, and leukopenia for dengue; eosinophilia for acute schistosomiasis; and splenomegaly and elevated serum alanine aminotransferase level for enteric fever.[5]

Siikamaki and colleagues reaffirm that a significant proportion of febrile returning travelers had a potentially life-threatening illness (about one-quarter). Bacteremia was as common as malaria. Also, the significant finding of several HIV cases warrants routine HIV testing. Both blood cultures and HIV tests should be considered in febrile travelers. Importantly, the high proportion of patients (10%) with more than one diagnosis highlights

the need for careful systematic work-up. A hospital-based study of the causes of fever in adults on the Thai-Myanmar border found that dual diagnoses were common, especially malaria (25% of the diagnoses) and leptospirosis (17%).[6]

In summary, fever is common in ill returned travelers and often results in hospitalization. The time of presentation and geographic region of exposure provide key information to generate the differential diagnoses. Particular symptoms and findings suggest some specific diagnoses. Travel medicine specialists who evaluate febrile returned travelers should evaluate the patient systematically, and include studies for malaria, blood cultures, and HIV tests especially in cases where localizing symptoms are lacking. ■

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Infectious Disease [ALERT]

Updates

By Carol A. Kemper, MD, FACP

Norovirus bounces between NBA players

Source: Desai R, et al. Transmission of norovirus among NBA players and staff, Winter 2010-2011. *CID* 2011; 53: 1115-1117.

Beginning in November 2010, players from several NBA teams were reported as suffering from the "stomach flu". An investigation was launched, querying 400 players and 378 staff members whether they had experienced nausea and/or vomiting sometime between November 10 and December 20. In total, 21 players and 3 staff members met the case definition for acute gastroenteritis from norovirus, based on the presence of symptoms with or without a positive RT-PCR stool test for norovirus. These 24 individuals represented 13 different teams from 11 different states.

The outbreak occurred between November 28 through December 8. Four teams had multiple cases with a total of 15 affected individuals. There was sufficient information available to indicate that 4 of these players were primary cases and 9 were secondary cases. Three of the four primary cases reported close contact with other members of the team during their illness, including contact in the locker rooms or travel together. One reported vomiting while en route to a game.

The authors identified 49 NBA games played during the 11-day outbreak. Two of these games were suspicious for team-to-team transmission of norovirus infection from a "donor team", with players with subsequently confirmed norovirus playing in those games. The authors examined 10 years of NBA "injury" data reports, and found that gastroenteritis was the second most common non-play-related injury in the NBA. They recommend that players with acute gastroenteritis symptoms be segregated from teammates, with restricted play, and strict personal hygiene and handwashing precautions during illness and for a good 24-72 hours after recovery. ■

A fluke of infertility ?

Source: Bailey SL, et al. Fluke Infertility: The late cost of a quick swim. *J Travel Med* 2011;18(1):61-62.

These authors describe two previously healthy, asymptomatic young British women who presented with upper genital tract disease, one during infertility work-up, which was surprising due to schistosomiasis acquired many years earlier.

The first was a 43 year-old woman undergoing infertility evaluation, including a normal hysterosalpingogram. Within a few weeks of that study, she developed suprapubic pain and cervical bleeding. Dense adhesions of the fallopian tube were observed laparoscopically, with what was described as "semi-solid calcified material" from the fallopian tube. Histopathology

revealed extensive granulomatous inflammation and Schistosoma haematobium were visualized.

Serological studies were positive. She had a remote history of travel to Egypt and Africa 8 years earlier, where she swum in Lake Malawi.

The second patient presented with acute lower quadrant pain; ultrasound identified two ovarian cysts. A torsed ovary was observed laparoscopically and she underwent a salpingo-oopherectomy. Histopathology revealed ovarian hemorrhage and granulomatous inflammation with giant cells and degenerating schistosomes. Her serology was also positive. She also had a remote history of travel to Africa 8 years earlier, and had swum in Lake Malawi.

Lake Malawi is an especially risky place for a quick swim: estimates suggest the risk of exposure is about 70% with one swim. Infection may remain asymptomatic until years later. Gynecological involvement is one of several presentations of "ectopic" schistosomiasis, although more commonly affects the cervix and vaginal area. However, the schistosomes can readily access the genital venous plexus, and cause upper genital infection, with inflammation and scarring years later. Chronic gynecologic infection may present with fistulae, pelvic pain, dysparunia, and infertility. ■

HIV and TB treatment: Together?

Source: Havlir DV, et al. Timing of antiretroviral therapy for HIV-1 infection and tuberculosis. *NEJM* 2011; 365; 16: 1482-1491.

When to initiate antiretroviral therapy (ART) in HIV-infected patients beginning treatment for tuberculosis has been a matter for debate. An open-label, randomized study comparing the benefits of early initiation of antiretroviral therapy (within 2 weeks of initiation of TB medication) versus delayed initiation of ART until 8-12 weeks following initiation of TB medication was conducted. A total of 809 HIV-infected patients with CD4 counts < 250 cells/mm3 with suspected tuberculosis who were beginning antimycobacterial therapy were randomized to either early or late initiation of ART. During the 48 weeks of observation, the risk of newly defined AIDS-related illness or death was similar between the two groups (12.9 vs 16.1% for the early-ART vs later-ART groups, p = 0.45). The most common AIDS-defined illnesses included cryptococcosis, esophageal candidiasis, and Kaposi sarcoma. Overall, 31 deaths occurred in the early-ART group and 37 deaths occurred in the later-ART group; more than half of which were HIV-related and none of which were related to TB infection. However, examination of the data for a prespecified subgroup of patients with CD4 < 50 cells/mm3 demonstrated a statistically significant greater risk of AIDS-related events and/or death in the later ART group compared with the early ART group (26.6% vs 15.5%, p = 0.02). A rationale for delaying initiation of ART has been the associated risk of TB-related immune reconstitution inflammatory sydrome (IRIS) with earlier initiation of ART. Patients in this study were observed to have a significantly lower risk of IRIS in the later ART group compared with the early ART group (5% vs 11%, p < .0001), although the numbers of patients with serious complications of IRIS were similar between the two groups. Prednisone was required to manage nearly half of the patients. Comparing the early vs. late ART groups, IRIS-related symptoms occurred a median of 4.6 and 11.7 weeks following initiation of TB treatment (much earlier in the early HIV treatment group). However, the duration of IRIS symptoms was similar between the two groups (about 69-75 days). Four of the 19 cases of IRIS in the late-ART treatment group occurred before the initiation of ART.

Treatment-related toxicity occurred with a similar frequency between the two groups. And both groups of patients had a similar response to antiretroviral therapy by 48 weeks of study.Slightly more than half (56%) of patients completed their TB treatment without modification or interruption, with no difference observed between the groups.

In conclusion, waiting 8-12 weeks to initiate ART in HIV-positive patients with CD4 counts between 50-250 cells/mm3 who are beginning TB treatment does not appear to significantly increase morbidity or mortality, and is associated with a reduction in IRIS-related events. However, patients with CD4 cells < 50/mm3 are at increased risk for AIDS-related events and mortality and should be started on ART as soon as possible, regardless of the increased risk for IRIS. ■

Clusters of respiratory illness from HEV68

Source: Centers for Disease Control and Prevention. Clusters of acute respiratory illness associated with human enterovirus 68 – Asia, Europe, and United States, 2008-2010. MMWR, *Morb Mortal Wkly Rep* 2011;60:1301-1304.

Human enterovirus 68 (HEV68) is one of the many summer-fall picornaviruses, but unlike its enteroviral cousins, seems to almost exclusively cause respiratory illness. Reports identify it as a rare cause of respiratory illness, often occurring in small clusters. This *MMWR* report documents the recent evidence for HEV68 respiratory infection in the Philippines, Japan, Netherlands and the United States. It identifies HEV68 as a more frequent cause of respiratory illness than previously recognized.

For example, during a clinical study of respiratory illness in pediatric patients hospitalized in the Philippines, specimens from 816 patients were retrospectively

screened for HEV68 by RT-PCR. Twenty-one (2.6%) were positive; 17/21 (81%) involved children ages 0-4, and two cases resulted in fatal respiratory infection. In the United States, adults admitted to a hospital in Atlanta with respiratory illness began being screened using a broad-based multi-pathogen testing system that includes entero-rhinovirus. Of 68 specimens testing positive for "ERV", 6 (8.8%) were positive for HEV68. Three of these 6 patients were 50 years or older, two were immunocompromised, five had fever and 4 cough; none of them developed respiratory failure or died. Similarly, at a pediatric hospital in Philadelphia, 390 children treated for respiratory illness were evaluated for HRV. Specimens from 66 subjects were submitted to the CDC for further testing, of which 15 (42%) were positive for HEV68. Half involved children ages 0-4, and 15 required admission to ICU .

Symptoms from HEV68 vary from mild respiratory symptoms to more severe respiratory failure; new-onset asthma, especially in a child may be present. Cases generally occur in late summer-fall. Clinicians should be aware that HEV68 may result in clusters of cases of viral respiratory illness. ■

CME INSTRUCTIONS

To earn credit for this activity, please follow these instructions:

1. Read and study the activity, using the provided references for further research.
2. Log on to www.cmecity.com to take a post-test; tests can be taken after each issue or collectively at the end of the semester. First-time users will have to register on the site using the 8-digit subscriber number printed on their mailing label, invoice or renewal notice.
3. Pass the online tests with a score of 100%; you will be allowed to answer the questions as many times as needed to achieve a score of 100%.
4. After successfully completing the last test of the semester, your browser will be automatically directed to the activity evaluation form, which you will submit online.
5. Once the completed evaluation is received, a credit letter will be e-mailed to you instantly.

CME QUESTIONS

1. Which of the following is correct?

A. The incidence of measles in Europe has been steadily decreasing.
B. Most cases of measles in Europe are occurring in Italy.
C. There is no indication for International U.S. travelers to maintain adequate measles immune status.
D. Population vaccination rates <95% can support continuing measles transmission.

2. Which of the following is correct with regard to current CDC recommendations for immunization of health care providers (HCP) against communicable infectious diseases?

A. All HCP, not just those involved in direct patient care, should receive annual influenza vaccination.
B. Pertussis (as Tdap) vaccine should not be administered to an individual who has received Td within the previous 5 years.
C. A history of prior measles infection is sufficient for a HCP to be considered immune; laboratory confirmation is not required.
D. A history of prior mumps infection is sufficient for a HCP to be considered immune; laboratory confirmation is not required.

3. The evaluation of fever in a traveler returning from the tropics:

A. should only include blood smears for malaria when the traveler did not take chemoprophylaxis.
B. may result in more than one diagnosis; hence, it requires a systematic work-up.
C. nearly always yields a pathogen, leading to specific causality.
D. is unlikely due to acute human immunodeficiency virus infection

CME OBJECTIVES

Upon completion of this educational activity, participants should be able to:

- discuss the diagnosis and treatment of infectious diseases;
- explain current data regarding the use of new antibiotics for commonly diagnosed diseases and new uses for traditional drugs;
- discuss the latest information regarding risks, benefits, and cost-effectiveness of new and traditional diagnostic tests; and
- discuss new information regarding how infectious diseases are transmitted and how such information can lead to the development of new therapies.

[IN FUTURE ISSUES]

Antibiotic lock therapy for IV catheter-associated gram negative bacteremia.

Risk factors for complications and mortality in patients with *Clostridium difficile* infection

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.*

Rivaroxaban Now Approved for Stroke Prevention

In this issue: New indication for rivaroxaban; new study on warfarin testing; medications causing adverse drug events; niacin as an add-on therapy; and FDA actions.

Rivaroxaban for atrial fibrillation patients

Rivaroxaban (Xarelto), Janssen Pharmaceutical's once-a-day oral Xa inhibitor, has been approved for reducing the risk of stroke in patients with atrial fibrillation. The drug was previously approved for prophylaxis of deep vein thrombosis in patients undergoing hip or knee replacement. Rivaroxaban is the second "non-warfarin" oral anticoagulant to be approved for this indication after the direct thrombin inhibitor dabigatran (Pradaxa). The approval was based on the ROCKET AF trial, a double-blind, randomized, noninferiority comparative trial with warfarin, which showed a rate of stroke or systemic embolism of 2.1% per year for rivaroxaban and 2.4% per year for warfarin. The study looked at 14,000 patients over 700 days of follow-up. Rates of major and non-major bleeding were the same with the two drugs, although the rate of intracranial hemorrhage was lower for rivaroxaban while the rate of GI bleeding was lower with warfarin. ROCKET AF showed noninferiority of rivaroxaban vs warfarin but not superiority (*N Engl J Med* 2011;365:883-891). The approval sets up a major marketing showdown between Janssen and Boehringer Ingelheim, the manufacturer of dabigatran, for this multibillion dollar market. Meanwhile, Pfizer and Bristol-Myers Squibb are jointly developing a third drug — apixaban, also a factor Xa inhibitor — which is undergoing an "accelerated review" by the FDA with approval likely in March 2012. All three drugs have the potential disadvantage of the lack of an antidote, a problem that seems to be plaguing dabigatran with more than 250 fatal bleeding episodes reported worldwide since the drug was approved in 2010. A recent report suggests that prothrombin complex concentrate may be an effective reversal agent for rivaroxaban but not dabigatran (*Circulation* 2011;124:1573-1579). ■

Warfarin testing every 12 weeks?

One of the major disadvantages of warfarin over the newer anticoagulants is the need for frequent prothrombin time monitoring and dose adjustment. Most guidelines recommend a maximum interval of 4 weeks between testing. A new study suggests that stable patients may be safely tested at 12-week intervals. A total of 226 patients who were on a stable dose of warfarin for at least 6 months were assigned to testing every 4 weeks, while the other half had blood tests done every 4 weeks, but sham INRs within the target range were reported for two of the three 4-week periods. The percentage of time in the therapeutic range was 74.1% in the 4-week group compared with 71.6% in the 12-week group (noninferiority $P = 0.020$ for a 7.5% point margin). Patients in the 12-week group had fewer dose changes and secondary outcomes, including major bleeding, thromboembolism, and death that were no different between the two groups. The authors conclude that assessment of warfarin dosing every

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12 weeks seems to be safe and noninferior to assessment every 4 weeks, although they recommend further study (*Ann Intern Med* 2011;155:653-659). This study is important given the marked cost differential between warfarin and dabigatran or rivaroxaban. Some patients, especially if they pay for their own medications, may opt to remain on warfarin if they are on a stable dose, especially if they only require testing four times a year. ■

Adverse drug events in the elderly

Although low cost, warfarin remains one of the most dangerous medications in common usage. In fact, hospitalizations for adverse events in the elderly are much more likely to be caused by commonly used medications, such as warfarin, rather than medications classified as high risk in the elderly, according to a new study from the CDC. Researchers used a national database of adverse drug events from 2007-2009 to estimate the frequency and rates of hospitalization after emergency department visits for adverse events in older adults to assess the risk of specific medications causing this hospitalization. It is estimated that adverse drug events led to nearly 100,000 hospitalizations during the 2-year period with nearly half among adults 80 years of age or older. Nearly two-thirds of the hospitalizations were due to unintentional overdoses. Four medications or medication classes were implicated alone or in combination in 67% of hospitalizations including warfarin (33.3%), insulins (13.9%), oral antiplatelet agents (13.3%), and oral hypoglycemic agents (10.7%). High-risk medications were implicated in only 1.2% of hospitalizations. The authors suggest that efforts to promote the safe management of antithrombotic and antidiabetic agents have the potential to substantially reduce harm to our older patients (*N Engl J Med* 2011;365:2002-2012). This study points out that we may be spending too much effort in managing "high-risk" medications in the elderly, while warfarin alone is responsible for a third of medication-related hospitalizations. ■

Is it time to retire niacin?

An editorial published online in the *New England Journal of Medicine* asks, "Niacin at 56 Years of Age — Time for an Early Retirement?" Retirement may be the logical next step after publication of the AIM-HIGH trial (see *Pharmacology Watch* July 2011), the National Heart Lung and Blood Institute's trial comparing niacin plus intensive statin therapy with intensive statin therapy alone in patients with established cardiovascular disease. The study was halted early when it was found that the addition of 1500-2000 mg of niacin per day to simvastatin, despite significantly raising HDL levels an average of 7 points, had no effect on the primary endpoint, which was a composite of the rate of death from coronary artery disease, nonfatal myocardial infarction, ischemic stroke, hospitalization for acute coronary syndrome, or symptom-driven coronary or cerebral revascularization (primary endpoint 16.4% niacin group, 16.2% placebo group; $P = 0.79$) (*N Engl J Med* published online November 15, 2011). The accompanying editorial suggests there is lack of evidence to support niacin as an add-on therapy in patients with cardiovascular disease who have well-controlled LDL cholesterol levels. Additionally, long-acting niacin is relatively expensive and frequently causes flushing — two additional factors that argue against continued use of the drug except, perhaps, in patients who are intolerant of statins (*N Engl J Med* published online November 15, 2011). ■

FDA actions

The news isn't much better for fenofibrate. The FDA has issued a safety communication for the cholesterol lowering medication stating that the drug may not lower the risk of major cardiovascular events based on data from the ACCORD Lipid trial. ACCORD (similar in design to AIM-HIGH) evaluated the efficacy and safety of fenofibrate plus simvastatin vs simvastatin alone in patients with type 2 diabetes. There was no significant difference in the risk of experiencing a major adverse cardiac event between the two groups, and women may have even experienced an increase in the risk for major adverse cardiac events with combination therapy vs simvastatin alone. The FDA is requiring the manufacturer of Trilipix brand fenofibric acid to conduct a clinical trial to evaluate the cardiovascular effects of the drug in patients at high risk for cardiovascular disease who are already taking statins (www.fda.gov/Drugs/DrugSafety/ucm278837.htm).

The FDA has approved a new formulation of zolpidem for treatment of insomnia in patients who wake up in the middle of the night and have difficulty returning to sleep. Zolpidem, originally marketed as Ambien and now available as a generic, is a short-acting hypnotic. The new product is a lower dose sublingual formulation that comes in a 1.75 mg dosage recommended for women and 3.5 mg for men. The lower dose for women is recommended because women clear the drug more slowly than men. It can be used if the patient has at least 4 hours of bedtime remaining. Zolpidem sublingual is marketed by Transcept Pharmaceuticals as Intermezzo. ■