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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

Community (Herd) Immunity Follows HPV Vaccination

By Hal B. Jenson, MD, FAAP
Dean, Western Michigan University School of Medicine, Kalamazoo, MI

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

SOURCE: Kahn JA, Brown DR, Ding L, et al: Vaccine-type human papillomavirus and evidence of herd protection after vaccine introduction. *Pediatrics* 2012;130:e249-e256.

Young women in two primary care clinics in Ohio who were from 13 to 26 years of age with a history of sexual contact were studied using a sequential sampling strategy in a pre-vaccination HPV surveillance study from 2006-2007 and in a postvaccination surveillance study from 2009-2010. Cervicovaginal swabs were genotyped for HPV using PCR amplification techniques. In the postvaccination study, participants were considered "vaccinated" if they had received at least one dose of the quadrivalent HPV vaccine.

There were 368 evaluable participants in the pre-vaccination surveillance study. Of the 409 evaluable participants in the postvaccination surveillance study, 242 (59.2%) had received at least one HPV vaccine dose, with a mean interval of 2.2 years since HPV vaccination.

The overall HPV prevalence rates among this cohort of sexually active young women increased during the 3-4 year interval of the study by 8.5%, from 68.3% to 76.8% ($P = 0.0003$). However, the prevalence of vaccine-type HPV among vaccinees decreased from 31.8% to 9.9% ($P < 0.0001$), and among non-vaccinees also decreased, from 30.2% to 15.4% ($P < 0.0001$). Subanalyses of only the high-

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risk vaccine-type HPV (HPV-16 and HPV-18) confirmed similar decreases.

The prevalence of high-risk nonvaccine-type HPV increased from 48.6% to 56.2% (P = 0.0038) for all participants. The increase in the rate of high-risk nonvaccine-type HPV was significant for vaccinated participants (P < 0.0001) but was not significant for unvaccinated participants.

COMMENTARY

This study was performed in a cohort of young women with high rates of HPV infection, and with continuing exposure as evidenced by the overall increased rate of HPV infections over the study period. The study confirms the effectiveness of quadrivalent HPV vaccine to reduce vaccine-type HPV prevalence rates. This study may actually understate the impact of HPV vaccination because only one HPV vaccine dose was required to be considered "vaccinated." A substantial reduction in vaccine-type HPV prevalence was seen not only among vaccinees, but also among unvaccinated persons. This demonstrates that quadrivalent HPV vaccination may provide significant community (herd) immunity even in a relatively limited timeframe of 4 years. Thus, HPV vaccination appears to reduce the prevalence of vaccine-type HPV among all young women in the community, which should translate to substantially decreased rates of cervical intraepithelial neoplasia (CIN) and cervical cancer. Although not included in this study, it is plausible that vaccine-type HPV prevalence rates among male sexual partners also decreased substantially in the community even though only young women were vaccinated. ■

Herpes Zoster Vaccine and the Incidence of Recurrent Herpes Zoster in the Elderly

By Richard R. Watkins, MD, MS, FACP

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Dr. Watkins reports no financial relationships in this field of study.

SYNOPSIS: In a matched cohort study involving immunocompetent individuals ≥ 60 years of age, the incidence of herpes zoster recurrence following a recent initial episode was low in both herpes zoster vaccine recipients and the unvaccinated. This low risk questions the need for vaccinating immunocompetent adults with recent herpes zoster infections.

SOURCE: Tseng HF, et al. Herpes zoster vaccine and the incidence of recurrent herpes zoster in an immunocompetent elderly population. *J Infect Dis* 2012;206:190-196.

A common question in clinical practice about the shingles vaccine is whether it is effective in preventing recurrent episodes in patients who have had herpes zoster (HZ). Currently the

Advisory Committee on Immunization Practices (ACIP) recommends it for patients ≥ 60 years of age, including those with prior HZ.[1] The actual risk of recurrence has not been elucidated, although it is thought to be higher in patients with more severe disease.[2] Since it was first licensed in 2006, the shingles vaccine has been hampered by production difficulties and shortfalls in availability. Although the Food and Drug Administration approved the shingles vaccine for adults aged 50 through 59 years in March 2011, the ACIP declined to follow suit, citing available evidence and the supply issues.[3] Healthcare policy-makers and providers therefore need guidance in determining shingles vaccination priorities.

To clarify these issues, Tseng and colleagues conducted a matched cohort study in the Kaiser Permanente system in Southern California. Members aged ≥ 60 years who received the shingles vaccine between 1/1/07 and 12/31/10 served as the vaccinated cohort. The unvaccinated cohort included randomly selected members who were matched 5:1 to the vaccinated group based on birth date (±1 year) and were assigned an index date that corresponded with the vaccination date of the matched vaccinated member. Both groups had the same selection criteria: (1) no diagnosis of HZ during 180 days prior to the date of vaccination; (2) they had a visit for a diagnosis of HZ that included a prescription of antiviral medication on the same day 180 to 730 days prior to vaccination; (3) they had not received a diagnosis of HZ ≤1 year prior to the index HZ case, defined as the first HZ case diagnosed in the reference period. Immunocompromised patients were excluded from both cohorts, including those with HIV, leukemia, lymphoma, or having been prescribed immunosuppressive agents during the period from ≤1 year before the index date until the end of follow-up. A propensity score was used to account for potential confounders and was created using a logistic regression model that predicted the probability of receiving the zoster vaccine. The study included 1036 vaccinated and 5180 unvaccinated subjects. Compared with the unvaccinated cohort, the vaccinated cohort had more female, white, and Asian members and a lower prevalence of chronic diseases. The incidence of recurrent HZ per 1000 person-years in those aged <70 years was similar in the vaccinated and unvaccinated cohorts, 0.99 (95% confidence interval (CI) 0.02-5.5) and 2.20 (95% CI 1.10-3.93), respectively. The unadjusted incidence rate ratio was 0.45 (95% CI 0.06-3.51; p = 0.45). There was a trend toward the incidence being lower in the vaccinated group, but the scarcity of events precluded the ability to detect a meaningful difference between the two cohorts.

There were a few limitations to the study. The authors did not confirm the initial HZ episode or the recurrence by laboratory testing. The cases were detected using electronic medical records, which could introduce bias from misclassification. Moreover, the incidence rate was calculated from the period from the index date (the first day of follow-up set by the vaccinated cohort) instead of the period starting from the previous episode. Thus, comparing the incident rate from this study to other studies is difficult and may be open to different interpretations.

COMMENTARY

As the authors describe, the occurrence of HZ is believed to result from a decline in a threshold level of varicella zoster virus (VZV) specific cell-mediated immunity. Ongoing exposures to VZV, both through endogenous and exogenous sources, may propagate effective VZV memory immunity. The shingles vaccine likely restores VZV-specific T cells to a level above the threshold. HZ and the shingles vaccine both generate a comparable VZV cell-mediated immunity that is protective against further episodes.[4] This study is important because it suggests that the risk of recurrent HZ following a recent initial episode is low among immunocompetent adults. Therefore, vaccination immediately following a recent HZ episode may not be necessary. But before this becomes routine

clinical practice, larger studies with longer follow-up and laboratory confirmation of cases need to be completed. Also, whether certain immunocompromised patients should be vaccinated following an episode of HZ remains an open question. Given the high cost of the vaccine and its frequent shortages, this study and future ones will hopefully aid policy makers and payers in prioritizing which patients should undergo vaccination. ■

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ABSTRACT AND COMMENTARY

Maraviroc and graft-versus-host disease

By Dean L. Winslow, MD, FACP, FIDSA
Chairman, Department of Medicine, Santa Clara Valley, Medical Center; Clinical Professor, Stanford University School of Medicine, is Associate Editor for Infectious Disease Alert.

Dr. Winslow is a consultant for Siemens Diagnostic.

SYNOPSIS: Maraviroc (MVC) inhibited CCR5 internalization and lymphocyte chemotaxis in vitro. 35 hematopoietic stem cell transplant (HSCT) recipients were treated with MVC starting 2 days prior to transplantation until day 30. In these patients grade II-IV acute graft- versus- host disease (GVHD) incidence was 14.7% at day 100 and 23.6% at day 180. Acute liver or gut GVHD was not observed before day 100 and remained uncommon through day 180.

SOURCE: Reshef R, et al. Blockade of lymphocyte chemotaxis in visceral graft-versus-host disease. *New Eng Jrl Med* 2012;367:135-145.

The CCR5 antagonist maraviroc (MVC) was tested in vitro to determine its effect on lymphocyte function and chemotaxis. 38 high-risk patients who underwent reduced intensity allogeneic HSCT were treated in a phase I/II pilot study using MVC twice daily (in addition to standard GVHD prophylaxis).

MVC inhibited CCR5 internalization and lymphocyte chemotaxis in vitro without impairing T-cell function or formation of hematopoietic-cell colonies. In 35 evaluable patients given MVC the cumulative incidence of grade II-IV acute GVHD was low at 14.7% by day 100 and 23.6% by day 180 and remained uncommon before day 180. The incidence of grade III-IV GVHD by day 180 was only 5.9%. The 1-year death rate (that was not preceded by disease relapse) was 11.7% without excessive rates of relapse or infection. MVC was well tolerated. Serum from patients receiving MVC demonstrated prevention of CCR5 internalization by CCL5 and blocked T-cell chemotaxis in vitro.

COMMENTARY

MVC is an interesting orally bioavailable small molecule inhibitor of the chemokine receptor CCR5 (whose natural ligands are MIP-1a, MIP-1b, and RANTES). The agent was specifically designed as an antiretroviral agent and has shown both in vitro activity and clinical utility in treating HIV-infected patients infected with strains of HIV which use the CCR5 coreceptor. It is not effective in patients infected with CXCR4-tropic strains of HIV. In contrast to other effective antiretroviral agents,

MVC actually binds to the cellular receptor rather than a viral target to produce its antiretroviral effect. MVC is not widely used as a component of HAART in the United States. This is likely due to the fact that other effective antiretroviral agents including second generation NNRTI's (etravirine), HIV protease inhibitors (darunavir), and integrase inhibitors (raltegravir) are now available as salvage therapy. While very well tolerated, MVC use is complicated by the fact that it must be dosed twice daily and it is only effective in patients infected with CCR5-tropic virus. The in vitro phenotype assay to determine HIV coreceptor usage costs $2,000 per assay and it often takes several weeks for the result to be available. In addition, while CCR5 coreceptor usage by HIV is common in early stage infection, CXCR4 coreceptor usage is more common in patients with more advanced HIV disease, further limiting use of MVC in treating HIV infection.

Despite initial concerns that blocking an important chemokine receptor would have serious adverse effects on the immune system, this has not been shown to be the case — probably due to the fact that there is much redundancy in this aspect of the human immune system. The only exception appears to be that individuals who are either homozygous or heterozygous for the CCR5 32 base pair deletion are susceptible to more severe infection with certain flaviviruses such as Yellow Fever and West Nile Virus.

One of the more problematic aspects of allogeneic HSCT is the need to "walk the knife edge" between engraftment (which repopulates the immune system and exhibits graft-versus-tumor effects) and GVHD. Visceral (especially GI) GVHD is a particularly severe complication and is a major cause of morbidity and mortality in HSCT recipients. This study shows that MVC (given for even a relatively short time — 30 days) appears to significantly inhibit lymphocyte trafficking and may be an effective new strategy to prevent visceral GVHD. Obviously larger studies (including randomized controlled trials) are needed to further validate this approach and to determine optimal duration of dosing. ■

ABSTRACT & COMMENTARY

Early Pet Contacts and Infant Respiratory Tract Illnesses

By Hal B. Jenson, MD, FAAP

Dean, School of Medicine, Western Michigan University School of Medicine, Kalamazoo, MI., is Associate Editor for Infectious Disease Alert.

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

SYNOPSIS: Infants having contact with a dog, and to a less extent with a cat, inside at home had fewer instances of respiratory tract symptoms and received fewer courses of antibiotics then infants without dog or cat contact.

SOURCE: Bergroth E, Remes S, Pekkanen J, et al: Respiratory tract illnesses during the first year of life: Effect of dog and cat contacts. *Pediatrics* 2012;130:211-220.

A birth cohort of 397 infants born from 2002 to 2005 in rural and suburban environments in Finland was followed through the first 44 weeks of life. Weekly

diary questionnaires gathered information on symptoms of infectious diseases as well as on the infant's dog and cat contacts. Information about pets included the type of pet and time spent inside daily. At the end of the study period, 65.2% of infants lived in homes with no dog contact and 75.5% lived in homes with no cat contact.

Only four infants were reported as having no respiratory symptoms during the entire 44-week study, and 62 infants (15.6%) were reported as asymptomatic for less than one-half of the weeks. In total, 285 (71.8%) infants reported fever, 384 (96.7%) rhinitis, 335 (84.4%) cough, 128 (32.2%) wheezing, and 157 (39.5%) otitis media at any time during the study. Fever was reported in 4.0% of study weeks, rhinitis in 17.0%, cough in 10.4%, wheezing in 2.0%, and otitis media in 2.5%. Nearly one-half of the infants, 189 (47.6%), required systemic antibiotics during the course of the 44-week study.

Of the 397 infants, 245 (61.7%) reported dog contact and 136 (34.3%) reported cat contact during the study. In univariate analyses, infants with dog or cat contacts were significantly healthier ($P < 0.001$) during the study period with fewer weeks of rhinitis, cough, and otitis media. These infants also required fewer courses of antibiotics compared to infants with no dog or cat contacts. In multivariate analyses, infants having a dog at home had significantly fewer respiratory symptoms, less frequent otitis media, and received fewer courses of antibiotics. The highest protective association was among infants with a dog inside at home for <6 hours a day. The associations did not change after removing from analysis those families (22.7%) who reported avoidance of pets and animals because of concern for allergies.

COMMENTARY

In this study, contact with a dog or cat inside the home during the first year of life provided a significant protective effect against respiratory tract symptoms and illness during infancy. Dog ownership provided a greater protective effect than cat ownership.

There is increasing evidence that animal contacts and frequent exposure to nature, such as living in a rural environment, especially during early life are crucial for developing non-allergenic immunity that provides protective effects against respiratory viral infections in early childhood. A completely protected environment, such as an urban lifestyle, that is free of traditionally common exposures during early life may actually impair development of protective immunity. The consequence of this protection during infancy appears to be manifest in more frequent respiratory tract illnesses and higher rates of asthma in childhood. ■

Nasal site MRSA surveillance may miss colonization

By Joseph F. John Jr. MD, FACP, FIDSA, FSHEA

Associate Chief of Staff for Education, Ralph H. Johnson Veterans Administration Medical Center; Professor of Medicine, Medical University of South Carolina, Charleston, is Co-Editor for Infectious Disease Alert.

SYNOPSIS: Nasal swabs identified only two-thirds of MRSA carriers.

SOURCE: Matheson A, Christie P, Stari T, et al. Nasal swab screening for methicillin-resistant Staphylococcus aureus—How well does it perform? A cross sectional study. *Infect Control Hosp Epidemiol* 2012;33:803-8.

David MZ, Medvedev S, Hohmann SF, et al. Increasing burden of methicillin-resistant Staphylococcus aureus hospitalizations at US Academic Medical Centers 2003-2008. *Infect Control Hosp Epidemiol* 2012;33:782-9.

The classic teaching is that if a human carries *Staphylococcus aureus*, it is most likely residing in the anterior nares. This concept held generally true for methicillin-susceptible *S. aureus* (MSSA) and for nosocomial methicillin-resistant *S. aureus* (MRSA) for many years. With the advent of community-based MRSA — so-called USA300 — there often was a conspicuous absence of nasal carriage in persons who had single or even multiple infections with community-MRSA/USA300. Thus, there has been an evolving question of what anatomic sites, if any, give the most reliable index of colonization and a risk of subsequent infection.

Now comes a study from Scotland in two of its acute care hospitals to determine which of four sites were the most likely to show colonization of MRSA at the time of admission. Four sites were swabbed for culture: nostrils, perineum, axilla and throat. Also a pooled swab was cultured in selective mannitol nutrient broth before being plated onto selective agar.
Of 12,889 admissions 6,533 patients were studied from Aberdeen Royal Infirmary and 3,781 from Crosshouse. When a positive wound or device culture was factored into the total positives, there were 298 positive colonizations. The nose was the most likely positive, (72.5%), followed by perineum (39.1%), throat (37.7%) and axilla (8.4%). The "gold standard" was the presence of at least one confirmed agar or broth/agar culture from any pooled swab. Nasal swabs identified 66% of the MRSA-positive admissions. Throat and perineal cultures add nearly 16%. Axillary cultures alone add only 2.4%.

COMMENTARY

Not all patients are Scots, but if they were, our current approach to pre-admission carriage of MRSA would have to change, or accept a recognition rate of just above two thirds. A rate of nearer to 50% may be true for a real world experience due to compliance, lack of standard training programs, etc. The Dutch routinely do nasal and throat swab looking for MRSA carriage and have reported throat carriage without nasal carriage previously. In the present study throat cultures plus nasal swabs would bring the screening accuracy to about 70%, not bad if a hospital wants to do something to recognize the MRSA carrier at admission and cohort these carriers. A positive culture of a preexisting infected site plus a nasal swab identified 100% of confirmed carriers.

The benefit of the study is to show that carriers may have colonization at one or more sites yet not have nasal colonization. The study also suggests that the nose is becoming less of a true focus of staphylococcal carriage, at least in terms of MRSA-colonized patients at the time of admission. The authors did a valiant job in organizing, implementing and analyzing the study and are to be congratulated for adding to this literature and to the Pathfinder study which is illuminating the role of MRSA in nosocomial infections. Of course the overall rate of MRSA carriage in these two Scottish hospitals at admission was only 3%. So, hospital administrators would have to be convinced that isolation of that small a MRSA-colonized group would actually prevent significant spread and morbidity in their hospitals.

Additionally, in an article accompanying the Scottish report, David and co-investigators from the University of Chicago found that there was a doubling of MRSA-associated hospitalizations from 20.9 per 1000 discharges to 41.7 per 1000 discharges. This sharp increase was likely due in part to infection with community MRSA, the very issue that the Scottish paper highlights by showing nasal swabs alone will not uncover those patients who are transporting community MRSA into the hospital. ■

Murine Typhus in Returned Travelers

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

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Dr. Blackburn is a Clinical Assistant Professor in the Division of Infectious Diseases and Geographic Medicine at Stanford University School of Medicine

Drs. Barry and Blackburn report no financial relationships to this field of study.

Synopsis: Murine typhus, caused by Rickettsia typhi and transmitted by the rat flea, has emerged as an etiologic agent of undifferentiated febrile illness in returned travelers. This retrospective study found that most cases of murine typhus at a well-known reference center in France were diagnosed in travelers returning from Africa or Southeast Asia.

SOURCE: Walter G, Botelho-Nevers E, Socolovschi C, et. al. Murine Typhus in Returned Travelers: A Report of Thirty-Two Cases. *Am J Trop Med Hyg* 2012;86:1049-53.

Murine typhus is an acute zoonotic infection caused by *Rickettsia typhi*, an obligate-intracellular Gram-negative bacterium belonging to the typhus group of rickettsiae. *R. typhi* infections occur worldwide, particularly in warm, humid coastal environments of the tropics; in the U.S., autochthonous transmission also occasionally occurs in Hawaii, Texas, and California. The rat flea, *Xenopsylla cheopis* is generally considered the primary vector. Humans are infected when rickettsia-laden flea feces are scratched into pruritic flea bite excoriations. The peri-domestic Rattus species is the critical vertebrate host that transmits the infection to fleas, although the rats do not usually show signs of illness even with high-level rickettsemia.

The authors at the World Health Organization Collaborative Center for Rickettsial Diseases in Marseilles, France retrospectively analyzed the epidemiological, clinical and biological characteristics of 32 patients with murine typhus who were diagnosed there during a three-year period (January 2008 to December 2010). A case was defined as a patient whose microimmunofluorescence serology was positive (single serum with IgM titer > 1:64 and/or IgG antibody titer > 1:128, or a >4-fold increase in titers between acute and convalescent sera). If cross-reactions were observed with other *Rickettsia* agents, a Western blot and cross-adsorption test were used to discriminate the species.

During the three-year study, 32 confirmed cases of murine typhus were discovered, and all were in returned travelers. During that time 42,276 sera were sent for evaluation to this reference laboratory for suspected rickettsial diseases from France and other countries. Thirteen (41%) of the 32 patients acquired murine typhus in Africa (Tunisia, Morocco, Ivory Coast, Central African Republic, Madagascar or Chad), and twelve (38%) acquired it in Southeast Asia (Indonesia, Philippines, Thailand, Cambodia, Vietnam, Myanmar or Laos). Tunisia and Indonesia were the two most common countries of exposure. The classic triad of fever, headache and rash was seen in only four patients, although a rash was present in 15 patients (47%). Elevated serum transaminases were found in over half the patients and represented the most common laboratory abnormalities. Cytopenias were observed in 12 (38%) of the 32 patients, and renal failure in three (9%) patients. Contact with rodents was rarely reported (n=2 of 32), and almost half of the cases were diagnosed in August or September, which seemed to correlate with flea abundance in endemic areas as well as a time of increased travel for Europeans. Fever was found in all patients for whom data

were available (31 of 31). Two patients had life-threatening illnesses, and three developed the hemophagocytic syndrome. All 32 patients recovered. The authors concluded that murine typhus should be considered a possible cause of febrile, undifferentiated illness in returning travelers.

COMMENTARY

Rickettsial diseases are increasingly being recognized among international travelers. In a Geosentinel study of almost 7,000 ill returnees with fever as a chief complaint, rickettsial disease was seen in 2%.[1] The taxonomy of *Rickettsia* species is fairly complex, but there are two species pathogenic for humans in the typhus group: *R. prowazekii* (epidemic louse-borne typhus) and *R. typhi* (murine typhus). Murine typhus, unlike African tick bite fever (caused by the spotted fever group rickettsia, *R. africae* — a relatively common cause of febrile illness in travelers returning from Southern Africa), does not present with a tell-tale eschar. Indeed, murine typhus is notoriously non-specific with fever, headache and an often poorly visible maculopapular exanthem; gastrointestinal symptoms appear to be common in children. The primary pathological lesion of *R. typhi* infection is an inflammatory vasculitis characterized by perivascular infiltration of lymphocytes, mast cells and macrophages. Thrombocytopenia and transaminitis are common. A recent report from Taiwan emphasized that fever with transaminitis is a clue to the diagnosis.[2] The incubation period of murine typhus is 8 to 16 days, and rash occurs near the end of the first week of illness — beginning on the trunk and spreading peripherally, sparing the palms and soles. The majority of patients experience mild illness, although, as reported in this article, illness can be severe. One patient presented with septic shock and another with myocarditis. As in other rickettsial diseases, the presence of G6PD deficiency, hemoglobinopathies such as thalassemia, and advanced age can be associated with severe or even fatal disease. Although spontaneous recovery can occur without treatment, the drug of choice for murine typhus remains doxycycline, to hasten recovery.

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Infectious Disease [ALERT]

Updates

By Carol A. Kemper, MD, FACP

Atypical hand, foot and mouth disease

Atypical Hand, foot and mouth disease (HFMD), California Update for clinicians, July 24, 2012; San Mateo County Public Health Advisory (1); *MMWR* Notes from the field: Severe hand, foot, and mouth disease associated with Coxsackievirus A6 – Alabama, Connecticut, California, and Nevada, November 2011- February 2012. March 30, 2012; 61(12); 213-214 (2); ProMEDmail alert, August 14, 2012 (3).

Health alerts in our area warn of local cases and small outbreaks of atypical hand, foot and mouth disease (HFMD) due to a novel strain of Coxsackievirus (1). A genetically similar strain was reportedly responsible for international outbreaks in northern Europe and Taiwan in 2008, but is now being reported in several states in the United States (2). Washoe County in Nevada has logged more than 400

self-reported cases atypical HFMD in the past few months, prompting an alert to school systems as the new school year starts (3).

Although Coxsackie viruses generally cause high fever and painful oral aphthi, with a rash on the palms and soles, most often in children, this strain seems to result in more severe and more generalized skin lesions, and has been affecting adults. From November 2011 to February 2012, 63 persons with HFMD with severe, atypical rash were reported to the CDC. Cases were reported from Alabama (n = 38) and Nevada (n = 17), California (n= 7), and one from Connecticut. Two-thirds of the cases occurred in children < 2 years of age, and one-fourth occurred in adults. Eight of the fifteen affected adults had exposure to an ill child, a contact of an ill child through day care, or had provided medical care to a sick child. While three-fourths of the patients were described with a rash on the hands, feet or mouth, 46% developed rash on the arms and legs, 41% had facial involvement, 25% had buttocks involvement, and 19% had rash on the trunk. Vesicles were reported in 70%, sometimes quite large or confluent, resembling bullae or blisters, and some of the lesions were hemorrhagic. Skin desquamation was common, and 2 patients shed their nails (onychomadesis). Nineteen percent of the patients required hospitalization, primarily for dehydration and/or pain control.

The rash may be so atypical that authorities caution it may be mistaken for Kawasaki's, varicella, disseminated HSV, eczema herpeticum, or vasculitis.

While most HFMD is due to Coxsackie A16, this strain has been identified, by molecular means, as a Coxsackievirus A6 (CAV6). Based on partial sequencing of the VP1 gene at the CDC and the California Department of Public Health laboratories, all 25 CVA6 strains tested appear closely related to strains identified in international outbreaks.

Public Health authorities recommend home isolation of suspect cases for at least 24 hours after fever resolution and once all lesions have healed or scabbed. Current monoclonal assays may miss this particular strain (commonly done for CAV16). Your local or state public health department laboratory may be prepared to do PCR testing or other specialized testing of throat or vesicle swabs (using a Dacron swab). People with active infection should avoid kissing or sharing utensils till lesions scab over and no lesions have appeared for 2 days. ■

Homelessness and TB a bad combination

Tuberculosis – USA: (Florida) fatal, homeless shelter. A ProMED-mail post, July 8, 2012; http://www.promedmail.org.

According to this ProMED-mail posting from July 2012, officials have expressed concern that an ongoing outbreak of tuberculosis in Jacksonville, Florida remains uncontained – and now threatens to spread to other parts of the state. This outbreak, which stemmed from a single individual with MTb in 2008, has now affected 99 individuals with active MTb, including 6 children, and resulted in 13 deaths. Hundreds to thousands of homeless and mentally ill in the Jacksonville area may have been infected.

Although not unusual for some parts of the world, this outbreak, which began in 2008, and was believed to have been contained at that time, and then obviously was not by 2011-2012, is emblematic of the degree to which one highly contagious individual, with unrecognized or poorly managed active MTb can infect hundreds of individuals. It is also no surprise this outbreak occurred coincident with the decline in public health funding. It is also a reminder that managing cases of active MTb in the homeless, mentally ill or drug addicted is not only especially challenging but of critical importance —and is exactly the circumstance where public health dollars are requisite.

The outbreak began in 2008, when a single patient with schizophrenia was

diagnosed with active MTb. A cough was documented in various charts for 8 months — but unfortunately he was variously admitted to jail, repeated psychiatric hospitalizations, homeless shelters, and an assisted living facility before his MTb was recognized and he was effectively quarantined at a State Tuberculosis Hospital (which has since been closed for lack of funding). From August 2008 — May 2009, 15 of the mentally ill residents of the assisted living facility and 3 other individuals at the psychiatric facility developed active MTb, 2 of whom died. Nine of the 18 isolates were available for testing; genotyping using spoligotyping and 12-locus mycobacterial interspersed repetitive unit typing (MIRU) showed the isolates to be identical (named FL046).

Investigation at the assisted living facility revealed that of the 75 residents, 88% had positive PPDs consistent with exposure. This rate of positivity suggests a high level of exposure in the facility. Based on this information, it has been estimated that up to 3000 to 4000 people at homeless shelters may have been additionally infected. Unfortunately, this report indicates that only 253 of those persons were ever identified and tested. The CDC provided Duval County with a grant ($USD275K) to facilitate the investigation, but once the funds ran out, personnel were apparently assigned to other duties.

It was not until an additional 30 cases were reported from Duval County in 2011 that authorities recognized the contagion had not been stemmed. Eleven of those cases were subsequently sent to the State TB hospital; and one remains quarantined at Jacksonville Memorial Hospital. These 30 cases also appear to be due to the same strain type. Fortunately none of the cases have demonstrated resistance to TB medications. Many of the subsequent cases have occurred in the homeless or mentally ill, who are undernourished, have poor and inconsistent access to medical care, and are especially hard to track. This report suggests that several of the deaths have occurred in poor black men, who simply presented with wasting, and were "too far gone" by the time their TB was recognized. ■

Chagas in Newborns

Congenital transmission of Chagas Disease – Virginia, 2010; *MMWR* July 6, 2012; 61(26): 477-479.

Awareness of Chagas in the blood supply in the United States — and in organ transplantation — as possible modes of transmission of this infection is increasing. Thus far only a handful of transfusion-related cases have been reported in the U.S. Data collected by the CDC suggests these cases are related to transfusion of fresh and not frozen blood products. Congenital transmission of Chagas in the U.S. seems to be similarly rare, in part because it is difficult to diagnose, there is a lack of awareness of the possible risk of infection, as well as a lack of classical signs and symptoms of neonatal infection.

This report documents the first case of congenital transmission of *Trypanosoma cruzi* in the U.S. A 31-year old mother from Bolivia required cesarean section for fetal hydrops at 29 weeks gestation. The baby weighed 1840 grams and had ascites, and pleural and pericardial effusions. An echocardiogram was normal, and no arrhythmias were noted. Studies for toxoplasmosis, malaria, cytomegalovirus, rubella, HSV, and enterovirus were negative, and the baby received empirical antibacterials and acyclovir.

The mother subsequently revealed she had been diagnosed with Chagas infection in Bolivia and had received antitrypanosomal treatment. The child's blood smear was positive for T. cruzi trypomastigotes. He responded well to a 60-day course of benznidazole, and by 10 months of appeared to developing normally.

Based on current epidemiological data, the numbers of at-risk women living in the U.S., and estimates of congenital transmission of 1%-5%,

approximately 65 to 315 cases of congenital T. cruzi transmission may be occurring every year in the U.S. Signs or symptoms of infection may be deceptive, varying from asymptomatic or subclinical infection to low birth weight, hepatosplenomegaly, anasarca, cardiac failure and respiratory distress, to meningoencephalitis. Treatment is usually curative in > 90% of cases if administered in the first weeks of life. ■

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. Maraviroc exacerbates graft-versus-host disease (GVHD) by blocking CXCR4 receptors allogeneic hematopoietic stem cell (HSCT) recipients.
B. Maraviroc appears to reduce cutaneous manifestations of GVHD but has no beneficial effect on visceral GVHD in HSCT recipients.
C. Maraviroc predisposes to mycobacterial infections in HSCT recipients.
D. Maraviroc appears to reduce the incidence of GVHD in allogeneic HSCT recipients.

2. Which of the following is correct regarding screening for MRSA colonization in patients admitted to acute care in Scotland in 2010?

A. Nasal swabs identify approximately one-third of those demonstrated to be colonized.
B. Nasal swabs identify approximately one-half of those demonstrated to be colonized.
C. Nasal swabs identify approximately two-thirds of those demonstrated to be colonized.
D. Nasal swabs identify approximately nine-tenths of those demonstrated to be colonized.

3. In which of the following states is transmission of Rickettsia typhi, the etiologic agent of murine typhus, known to occur?

A. None – such transmission does not occur within the United States.
B. Hawaii, California, and Texas.
C. California, Arizona, and Texas.
D. California, New Mexico and Texas

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]

Randomized Trial of Probiotics and Calcium on Diarrhea and Respiratory Tract Infections in Indonesian children.

Antibiotic Concentrations During Continuous Renal Replacement Therapy

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.*

Does Finasteride Cause Permanent Sexual Side Effects?

In this issue: Side effects of finasteride; new ruling on pharmaceutical companies paying generic manufacturers; and FDA actions.

Sexual side effects of finasteride

Finasteride — the popular drug used to treat male pattern baldness and symptomatic benign prostatic hypertrophy — may cause long-term sexual dysfunction, according to a new study. Several recent studies have shown that the drug, which is marketed as 1 mg (Propecia) and 5 mg (Proscar), can cause sexual side effects that persist after stopping the drug in as many as 20% of men. In April, the FDA required new labeling for both strengths regarding libido, ejaculation, orgasm disorders, and even infertility that may persist after treatment ends. The new study looked at 54 men, with an average age of 31, who reported ≥ 3 months of sexual side effects after taking the 1 mg strength for male pattern baldness. All men were previously healthy without previous history of sexual dysfunction, medical conditions, psychiatric conditions, or prescription medication use. After 9-16 months of follow-up, 96% of subjects reported persistent sexual side effects (based on the Arizona Sexual Experience Scale). The duration of finasteride use did not correlate with changes in sexual dysfunction scores. The authors urge prescribers of finasteride to warn men of potential adverse effects (*J Sex Med* published online July 12, 2012). ■

Pharmaceutical company ruling

Is it legal for pharmaceutical companies to pay generic manufacturers to keep their products off the market? Until now it has been. Brand-name manufacturers have written enormous checks to keep their low-cost generic competitors off the market. That may change, however, after a federal appeals court in Philadelphia ruled that the practice is anticompetitive, a decision that is counter to three previous federal circuit courts rulings. *The New York Times* cites the example of Bayer Pharmaceuticals which paid generic drug maker Barr Laboratories and other generic houses $400 million to withhold their generic version of ciprofloxacin, their $1 billion a year blockbuster antibiotic. The case could eventually end up at the Supreme Court. At stake is billions of dollars in lost profits for pharmaceutical manufacturers, but an equal amount of savings for Medicare/Medicaid, health plans, and consumers. ■

FDA actions

The FDA has approved the second new weight-loss medication within a month. The new product combines phentermine along with topiramate in an extended-release product. Phentermine has been marketed since 1959 and was part of the infamous "fen-phen" combination that was popular in the 1990s (fenfluramine was eventually banned due to cardiac valvulopathy in 1997). Topiramate is currently marketed as an anticonvulsant and for migraine prophylaxis as Topamax. The combination was rejected by the

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FDA in 2010 due to safety concerns, but Vivus Pharmaceuticals submitted additional data to the agency and recently won approval in July. In the process, the company changed the brand name from Qnexa to Qsymia. Similar to the recently approved lorcaserin (Belviq), phentermine/topiramate is approved as an addition to a reduced-calorie diet and exercise for weight management in adults with a BMI of 30 or greater, or with a BMI of 27 or greater with at least one weight-related condition such as hypertension, type 2 diabetes, or dyslipidemia. In two placebo-controlled trials, 3700 obese and overweight patients lost an average of 6.7-8.9% of their body weight, depending on the recommended or higher dose therapy (slightly better results than those seen with lorcaserin). Patients who have not lost at least 3% of their body weight by week 12 should discontinue the drug. Because of continued safety concerns, the drug was approved with a Risk Evaluation and Mitigation Strategy (REMS), which consists of a medication guide, prescriber training, and pharmacy certification. The drug cannot be used during pregnancy or in patients with recent stroke or heart disease, and patients should have their heart rates monitored during therapy. Vivus will market Qsymia immediately, but will be required to conduct 10 postmarketing studies to assess safety.

The FDA has approved aclidinium bromide, a dry powder inhaler for long-term maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD). Aclidinium is a long-acting antimuscarinic agent that works primarily on the M3 receptor causing sustained bronchodilation. The approval was based on three studies of nearly 1300 patients with COPD. The drug may cause anticholinergic side effects, including worsening narrowing-angle glaucoma and urinary retention. It should not be used as a rescue inhaler and is not recommended for those 18 years of age or younger. It is dosed twice a day. Aclidinium inhaler is the second anticholinergic inhaler to be approved after tiotropium (Spiriva), which was approved in 2004. Aclidinium will be distributed by Forest Laboratories and will be marketed as Tudorza Pressair.

The FDA has approved mirabegron to treat adults with overactive bladder. The drug is a novel, once-daily beta-3 adrenergic agonist that works by enhancing storage function and relaxing the urinary bladder, a unique effect and distinct from currently marketed antimuscarinics that inhibit bladder contraction. The once-a-day medication will be available in 25 mg pills. The dose can be increased to 50 mg after 2 months if needed. The approval was based on three placebo-controlled trials that showed statistically significant improvement in incontinence episodes and number of urinations per 24 hours. The most common adverse effects were hypertension, nasopharyngitis, urinary tract infection, and headache. Mirabegron will be marketed by Astellas Pharma as Myrbetriq.

The FDA has approved a new colon cleansing agent for colonoscopy prep. The new prep is sodium picosulfate, magnesium oxide, and citric acid in powder form that is dissolved in water and taken in two doses the night before and the morning of the procedure. It may also be taken the afternoon and the evening before the procedure (Day-Before regimen). The safety and efficacy of the new agent was studied in two studies of about 1200 patients undergoing colonoscopy in which standard PEG plus electrolytes was used as a comparator, and the new prep was found to be at least as effective as the standard prep. Ferring Pharmaceuticals will market the new two-dose prep as Prepopik.

The FDA has approved icosapent ethyl, a new fish oil preparation for the treatment of hypertriglyceridemia. It is approved as an adjunct to diet to treat patients with triglyceride levels greater than 500 mg/dL. The drug contains ultra purified ethyl EPA, an omega-3 fatty acid. The new product follows GlaxoSmithKline's Lovaza, another fish oil that is currently marketed for the same indication and generates more than $1 billion in annual sales. The new product is manufactured by Amarin Corporation and will be marketed as Vascepa. Fish oils are effective at lowering triglycerides but evidence is lacking that they are effective for secondary prevention of cardiovascular disease (*Arch Intern Med* 2012;172:686-694).

An FDA advisory committee has recommended an new indication for Genentech's ranibizumab (Lucentis) for the treatment of diabetic macular edema, an indication for which there is currently no approved therapy. The drug is approved to treat neovascular age-related macular degeneration and macular edema following retinal vein occlusion. Diabetic macular edema is commonly treated with laser therapy, a procedure that has the potential side effect of some vision loss. The FDA generally follows its advisory committee's recommendations and should make a final recommendation later this year. ■