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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

A New Human Coronavirus Causing SARS-Like Illness: WHO Casts Wide Net, no Definitive Human-to-Human Transmission

By Stan Deresinski, MD, FACP, FIDSA

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SOURCE: Zaki AM, et al. Isolation of a novel coronavirus from a man with pneumonia in Saudi Arabia. *New Engl J Med* 2012;367:1814-20

On June 13, 2012, a 60-year-old Saudi man was admitted to a hospital in Jeddah, Saudi Arabia, with severe pneumonia after 7 days of fever and worsening respiratory symptoms. Following transfer to intensive care the following day, he required mechanical ventilation but died due to progressive respiratory and renal failure on hospital day 11. Various bacteria had been isolated from respiratory secretions during his hospitalization, but examination by indirect inmmunofluorescence for common respiratory virus pathogens was negative. Cytopathic effects were observed in LLC-MK2 cells inoculated with sputum obtained on the day of hospital admission and the patient's serum collected on hospital days 10 and 11 strongly reacted to infected cells in an IgG immuofluorescence assay – a finding not duplicated in 2400 samples from patients seen in Jeddah. While PCR assays for other respiratory virus families were negative, amplicon fragments were generated with primers designed to detect coronaviruses. Examination of the results

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of sequencing identified a novel betacoronavirus most closely related to 2 bat coronaviruses, called hCoV-EMC/2012 (human coronavirus- Erasmus Medical Center, the latter indicating the Rotterdam, Netherlands institution at which the viral discovery was performed, although the initial isolation in cell culture was performed in Saudi Arabia).

On September 23, authorities in the United Kingdom reported that the same virus had been detected in a 49-year-old Qatari with a severe respiratory infection who had been transferred to England for intensive care. Since then additional cases have occurred. On November 30, the World Health Organization reported that 2 fatal cases in Jordan occurred in April, 2012, but the virus had only recently been identified as the cause. Overall to date, a total of 9 laboratory-confirmed cases of infection with the novel coronavirus have been reported to WHO — five cases (including 3 deaths) from Saudi Arabia, two cases from Qatar and two cases (both fatal) from Jordan. The infections in each case had been locally acquired and, although there have been 2 clusters — a family in Riyadh and hospital health care workers near Amman — there is as yet no definitive evidence of human-to-human transmission.[1]

■ COMMENTARY

WHO recommends that infection with this virus should be suspected in patients with pneumonia or ARDS without an alternative etiologic diagnosis and who have a history of residence in or travel to the Arabian Peninsula within previous 10 days.[2] Also suspect are individuals with acute respiratory illness of any severity who have had close contacts with patients with proven or suspected hCoV-EMC/2012 infection within the previous 10 days. In addition, case clusters of severe respiratory infection of unknown etiology — whether or not the patients have traveled to the Arabian Peninsula — should also be suspect. Similarly suspect are health care workers with pneumonia who have cared for a patient with severe respiratory symptoms without etiological diagnosis and without regard to travel history. Thus, WHO has cast quite a wide net.

Prior to the 2003 SARS outbreak, only 2 human coronaviruses (which caused only cold symptoms) were known, but subsequent to that outbreak, 2 additional ones (HCoV-NL63 and HCoV-HKU1) were soon identified. HCoV-EMC now represents the sixth coronavirus known to cause disease in humans. The illness caused by this virus resembles that caused by the SARS virus, but sequencing has demonstrated that the viruses are only distantly related. A major difference from SARS is that the latter was very efficiently transmitted between humans, which, to date, does not appear to be the case with this new coronavirus. It should also be recognized with regard to this new virus that Koch's postulates — the criteria establishing a causal relationship between a microbe and a disease — have not been formally fulfilled. ■

References

1. WHO. Global Alert and Response (GAR). Novel coronavirus infection – update http://www.who.int/csr/don/2012_11_30/en/index.html
2. WHO. Interim surveillance recommendations for human infection with novel coronavirus.
3. December 2012http://www.who.int/csr/disease/coronavirus_infections/InterimRevisedSurveillanceRecommendations_nCoVinfection_03Dec12.pdf

Upon Further Review: Femoral Venous Catheters Do Not Increase Risk of Catheter-Related Bloodstream Infection

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 meta-analysis, investigators found that recent studies show no difference in the risk of catheter-related bloodstream infections between internal jugular, subclavian, and femoral sites. Older studies had a lower risk for the internal jugular site compared to the femoral site.

SOURCE: Marik PE, et al. The risk of catheter-related bloodstream infection with femoral venous catheters as compared to subclavian and internal jugular venous catheters: A systemic review of the literature and meta-analysis. *Crit Care Med* 2012;40(8):2479-85.

Catheter-related bloodstream infections (CRBSIs) cause significant morbidity and mortality. They are also very costly, approximately $50,000 per infection, for which hospitals are not reimbursed by Medicare and Medicaid. It is widely believed that the femoral site is less safe in terms of infection risk compared to the subclavian (SC) and internal jugular (IJ) sites. Indeed, guidelines from the CDC and IDSA on preventing CRBSIs advise against using the femoral vein for central access.[1,2] In order to evaluate the evidence behind this recommendation, Marik and colleagues performed a systematic review and meta-analysis comparing the risk in adults for CRBSIs for catheters placed in the femoral vs. internal jugular and subclavian sites.

The authors identified studies published between 1966 to October 2011 that reported the rate of CRBSI at the femoral, SC and/or IJ sites. They sub-grouped according to study design and assessed heterogeneity and bias. Two randomized controlled trials and eight cohort studies were included in the meta-analysis. There was no significant difference in risk for CRBSI between the femoral and SC sites (RR 1.75, 95% CI 0.80-3.8, P = .16). Meta-regression showed a significant interaction between the risk of infection and year of study publication, where earlier studies favored the SC site (P = .05). Overall, the IJ site was associated with a significantly reduced risk for CRBSI compared to the femoral site (RR 1.90, 95% CI 1.21-2.97, P = .005). However, when two outlier studies were removed from the analysis there was no significant difference between the femoral and IJ sites (RR 1.35, 95% CI 0.84-2.10, P = .2). Meta-regression again demonstrated a significant interaction between year of publication and risk for infection, with earlier studies favoring the IJ site (P = .01). There was no significant difference in CRBSI rate between the SC and IJ sites (RR 1.09, 95% CI 0.67-1.75, P = .74). Finally, there was no difference in risk for deep vein thrombosis (DVT) between the femoral site and the IJ and SC sites combined. Significant heterogeneity was found between the studies. ■

■ COMMENTARY

Conventional wisdom teaches that the SC vein is superior to the IJ for preventing CRBSIs, which in turn is superior to the femoral vein. The findings of the present study i.e. recent data show no difference in risk of CRBSIs between the femoral, IJ and SC sites, challenge this belief as well as current guideline recommendations about avoiding the femoral site. Moreover, a recent Cochrane review also found no difference in CRBSI rate among the three insertion sites.[3] Except for certain patients for whom the femoral site should be avoided (obese, renal transplant recipients, on chronic hemodialysis), Marik and colleagues recommend that insertion sites be chosen based on the lowest likelihood of injury.

This study does have several limitations. First, one of the RCTs was conducted before the

line-bundle standard was implemented and the other did not include patients with a body mass index greater than 45. It seems intuitive that changes in line insertion techniques in recent years, such as improved hand hygiene, use of chlorhexidine for skin decontamination, full-body drapes, catheter-insertion checklists, and ultrasound guidance for placement are a major cause for declines in CRBSI rates. Second, they did not distinguish between CRBSI and catheter colonization rate, as not all colonized catheters necessarily equal clinical infection. Third, the authors used data that combined outcomes for standard and antimicrobial catheters. Finally, the incidence of DVT may have declined over time due to heparin usage as part of the ventilator bundle.

Is it time to abandon the axiom about avoiding femoral central lines? Probably not yet, although the practice does seem safer now than in the past. As Marik and colleagues acknowledge, the rate of CRBSIs in the U.S. has declined from 5.32/1,000 catheter days in 1998 to 2.05/1000 catheter days in 2009. It is possible that this is due in part to clinicians not using the femoral site, but more likely it is from better catheter insertion practices. However, it may be time to re-examine current guideline recommendations and at least acknowledge that the femoral site might be an option, with the caveat that the final decision about site placement requires a careful analysis of the risks and benefits. ■

References

1. O'Grady NP, et al. Guidelines for the prevention of intravascular catheter-related infections. *Clin Infect Dis* 2011;52:e162-93.
2. Marschall J, et al. Strategies to prevent central-line associated bloodstream infections in acute care hospitals. *Infect Control Hosp Epidemiol* 2008;29(Suppl1):S22-S30.
3. Ge X, et al. Central venous access sites for the prevention of venous thrombosis, stenosis and infection. *Cochrane Database Syst Rev* 2012;3:CD004084.

ABSTRACT & COMMENTARY

Invasive Mold Infections Following Trauma

By Dean L. Winslow, MD, FACP, FIDSA

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Dr. Winslow is a consultant for Siemens Diagnostic

SYNOPSIS: Invasive mold infections were encountered in 37 patients following combat injuries sustained between June 2009 and December 2010. Mucorales, Aspergillus and Fusarium species predominated in this series. A second report describes 13 patients who developed necrotizing cutaneous Mucormycosis following injuries sustained in a tornado in Joplin, Missouri in 2011.

SOURCES: Warkentien T, et al. Invasive mold infections following combat-related injuries. *Clin Infect Dis* 2012; 55:1441-9.

Fanfair, RN, et al. Necrotizing cutaneous mucormycosis after a tornado in Joplin, Missouri, in 2011. *New Engl Jrl Med* 2012; 367:2214-25.

Thirty-seven cases of invasive fungal infection (IFI) were identified among US military personnel injured during combat in Afghanistan from June 2009-December 2010. Of these, 20 demonstrated histopathological angioinvasion, 4 showed nonvascular tissue invasion, and 13 had positive fungal cultures without histopathological evidence of tissue invasion. During the last quarter of 2010 rates of IFI reached 3.5% of trauma admissions. Blast injury was the etiology of injury in 100% of patients and occurred while conducting foot patrols in 92%. Ninety-four percent of the injuries were sustained in southern Afghanistan. Eighty percent sustained lower extremity amputation and 97% of patients underwent large volume blood transfusion. Mold isolates were recovered in 83% of cases (order Mucorales, n=16; Aspergillus species, n=16; Fusarium species, n=9; and multiple mold species in 28% of cases). Outcomes included 3 infection-related deaths (8%), additional debridements were required in 11 cases and amputation revisions in 58%.

Thirteen cases of invasive cutaneous Mucor infections were identified following the 2011

tornado which struck Joplin, Missouri. Five patients (38%) died. Case patients sustained a median of 5 wounds, 11 patients had at least 1 fracture, 9 sustained blunt trauma and 5 had penetrating trauma. Sequencing of D1-D2 region of 28S rDNA was consistent with Apophysomyces trapeziformis in all 13 case patients.

■ COMMENTARY

Invasive fungal infections are emerging as an increasingly important trauma-related infection. In both case series extensive soft tissue and/or cutaneous trauma was the most important underlying factor. As in the recently-concluded war in Iraq, more than 75% of combat injuries and deaths in Afghanistan are due to blast injuries from improvised explosive devices (IED's). In Iraq after about 2005 most of the serious injuries were due to sophisticated explosively-formed penetrator (EFP) devices (generally fielded by Iranian-backed Shia splinter groups) often triggered by passive infrared (PIR) windows and the injuries were often sustained by soldiers in tactical vehicles. In Afghanistan, apparently EFP's are still relatively uncommon, but soldiers on dismounted (foot) patrols are commonly gravely injured by huge relatively primitive IED's (Calcium ammonium nitrate is readily available for agricultural use in Afghanistan) with pressure-plate triggers. In both cases soldiers injured by IED's often sustain multiple limb amputations and extensive burns.

Modern combat injury management includes aggressive debridement of devitalized tissue and irrigation, as often as every 48 hours with delayed wound closure. The 3.5% rate of IFI's in this population seems remarkably low. Gross contamination of these wounds at the time of injury with dirt and other organic material is almost universal and is obviously the source of molds in these patients. While the 1.3% rate of IFI's seen among the approximately 1,000 patients injured in the Joplin tornado seems low, it is probably comparable to the US military experience if controlled for degree of injury severity and soft tissue damage.

In any case, awareness of IFI as a complication of severe soft tissue injury is important. Appropriate management includes aggressive surgical debridement and when appropriate early institution of systemic antifungal therapy. Pending identification of the fungal pathogens in these cases, empiric use of both liposomal Amphotericin B plus an antifungal triazole such as voriconazole seems appropriate since Mucor species are often resistant to triazoles and Aspergillus terreus is resistant to Amphotericin B. ■

ABSTRACT & COMMENTARY

Differences in Travel-Associated Diseases between Older and Younger Adults

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

SYNOPSIS: This study analyzed prospective data from 1997 to 2009 on ill international travelers. Compared to younger travelers, those 60 years and older had a higher incidence of lower respiratory infections, high-altitude pulmonary edema, phlebitis and pulmonary embolism, arthropod bites, severe malaria, rickettsiosis, gastritis, peptic ulcers, esophagitis and gastroesophageal reflux disease, trauma and injuries, urinary tract infections, heart disease, and death.

Source: Gautret P, et al. Travel-Associated Illness in Older Adults (>60 y). *J Travel Med* 2012;19:169-77.

Currently adults aged 60 years and older represent 15%-30% of international travelers. This age group is believed to be at increased risk for travel-related illnesses for several reasons, including their increased probability of underlying medical conditions, waning immunity from previous vaccinations, reduced immune response to vaccines given

prior to their trip, and a greater predisposition to acquiring certain diseases. Indeed, this is well known by those in the insurance industry who regularly charge older travelers much higher premiums than their younger counterparts. In this study, investigators sought to determine the range of illnesses among older adult travelers. They utilized prospective data from patients who presented to GeoSentinel sites from March 1997 to August 2009.

The GeoSentinel Surveillance Network is a group of travel medicine clinics on six continents where ill travelers are seen during or after traveling to a range of destinations. Patients were eligible to be included in the database if they crossed an international border and sought medical advice at a GeoSentinel clinic for a presumed travel-related illness, or had been diagnosed with a disease related to travel history by the clinic physician. Data collected included demographic information, travel data, reason for travel, inpatient or outpatient status, history of a pre-travel clinic visit, and travel-related clinical findings. Co-morbid illnesses and chronic conditions were not documented in the database.

A total of 63,076 ill adult travelers were included in the database, of which 7,034 were aged 60 years and older (8.4%). Compared to younger travelers, older patients were more likely to be male, reside in North America, travel for tourism, travel for a shorter duration, and less likely to have sought travel advice before their trip. Acute diarrhea was the most common illness in both groups, although it was comparatively less frequent among the older travelers. Respiratory illness was the second most common condition in the older group, while febrile systemic illness was second in the younger travelers. Illnesses that were significantly more common in the older group included lower respiratory tract infections, high-altitude pulmonary edema, arthropod bites, Plasmodium falciparum severe malaria, rickettsiosis, gastritis, peptic ulcer, gastroesophageal reflux disease, strongyloides, trauma and injuries, altitude sickness, vertigo, cerebrovascular accident, urinary tract infections, heart disease, phlebitis, pulmonary embolism, and death. Subanalysis revealed an inverse relationship between age and P. falciparum malaria and dengue among ill travelers ($p < 0.001$).

The main strength of this study was its multicenter design, which allowed for a large number of participants from many countries. It was limited because the data collected may not be representative of the overall population of travelers, and the results may not be generalizable to the illnesses usually seen at non-specialized primary care offices where mild or self-limited conditions present with more frequency. Also, underlying chronic diseases were not documented by GeoSentinel which does not allow evaluation of their impact on travel-associated morbidity. The authors concluded that older travelers have a higher relative proportion of life-threatening illnesses (lower respiratory tract infection [LRTI], high-altitude pulmonary edema, severe P. falciparum malaria, cardiovascular disease, and pulmonary embolism) and should be specifically targeted for prevention of such diseases.

■ COMMENTARY

It has become common to see adults aged 60 years and older in travel clinics. Individuals in this age group are believed to be at higher risk for travel-associated illnesses.[1] Hence, it seems prudent that specific travel advice tailored to this age group be established, in addition to other routine precautions and interventions (i.e. vaccines) given to all travelers. The study by Gautret and colleagues provides useful data towards building this base of recommendations. It was a large multicenter study that used data collected from the GeoSentinel Surveillance Network, which is supported by the Centers for Disease Control and Prevention. The authors found that the spectrum of illnesses varied widely depending on the age of travelers after eliminating confounding factors, such as travel destination. Older travelers suffered more morbidity from age-related conditions, such as cardiovascular diseases. Another recent study confirmed this observation, wherein the main cause of death in travelers over age 65 was cardiovascular (70%), followed by infectious disease (12%).[2] It was interesting that acute diarrhea occurred with less frequency in the group of older travelers. The authors speculate this was due to an increased likelihood of past exposure to pathogens or better adherence to reduced risky dietary exposures. Alternatively, the older travelers may have taken antibiotics and/or antimotility agents with more frequency. Given their greater proportionate morbidity from LRTIs, older travelers should take precaution against respiratory illnesses. The authors suggest good hand hygiene, use of disposable handkerchiefs, and face-masks in crowded conditions. Influenza was the

most common vaccine-preventable disease in the study, supporting the recommendation that all travelers be given the influenza vaccine. Pneumococcal vaccination is another intervention older travelers can do to lessen their risk for LRTI, as can younger travelers with chronic illnesses. With the higher risk for severe illness from P. falciparum malaria in older travelers, malaria chemoprophylaxis along with insect repellant and mosquito nets should be emphasized. ■

References

1. Cooper MC. The elderly travelers. *Travel Med Infect Dis* 2006;4:218-222.
2. Lawson CJ, et al. Deaths in international travelers arriving in the United States, July 1, 2005 to June 30, 2008. *J Travel Med* 2012;19:96-103.

ABSTRACT & COMMENTARY

Hepatitis B and C Screening

By Lin H. Chen, MD

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

SYNOPSIS: Adults with private healthcare insurance in the US have suboptimal testing for chronic HBV and HCV. Clearly, increased awareness is needed regarding HBV and HCV infections, epidemiology, risk, and screening.

SOURCE: Spradling PR, et al. Hepatitis B and C virus infection among 1.2 million persons with access to care: Factors associated with testing and infection prevalence. *Clin Infect Dis* 2012;55(8):1047-55.

This observational cohort study was conducted among 1.25 million adults from 4 private US healthcare organizations (HCO): Geisinger Health System, Danville, Pennsylvania; Henry Ford Health System, Detroit, Michigan; Kaiser Permanente-Northwest, Portland, Oregon; Kaiser Permanente, Honolulu, Hawaii. The study included persons who had ≥1 clinical encounter during 2006-2008 and ≥12 months of follow-up before 2009. The data on infections from this cohort was compared with those from the National Health and Nutrition Examination Survey (NHANES).

Hepatitis B virus (HBV) testing was done on 18.8% of 866,886 persons without a previous diagnosis, resulting in a 1.4% positive rate. Hepatitis C virus (HCV) testing was done on 12.7% of 865,659 persons without previous diagnosis, resulting in 5.5% positive. Among persons with at least 2 abnormal serum alanine aminotransferase (ALT), less than half were tested for HBV or HCV. Tests found that Asians were most likely to be infected with HBV (adjusted OR 6.33 compared to whites) whereas persons aged 50-59 years were most likely to be infected with HCV (adjusted OR 6.04 compared to age <30 years). The investigators estimate from NHANES that nearly ½ of HCV and 1/5 of HBV infections still remain unidentified.

■ COMMENTARY

It is estimated that 1-2% of the US population has chronic HBV or HCV infection, about 3.5-5.3 million persons, or 3-5 times more frequent than HIV infection. Among them, about 800,000-1.4 million have chronic HBV while 2.7-3.9 million have chronic HCV.[1] The last few years have brought advances in treatment for both HBV and HCV (for example, tenofovir, entecavir, telaprevir and boceprevir), and early therapy of chronically infected persons may provide sustained virologic response.

Both HBV and HCV are blood-borne infections. HBV can be transmitted vertically from infected mothers to infants during birth, as well as via sexual contact, sharing needles, and needle stick injuries. Foreign-born persons from endemic countries have an increased likelihood of being chronically infected. Asians and Pacific Islanders are the predominant groups of Americans with chronic HBV infection as well as having a disproportionately high incidence of hepatocellular carcinoma (HCC).[2] However, African-American adults have the highest rate of acute infection, particularly in the South.

HCV is usually transmitted via percutaneous blood exposure, including receipt of a blood

transfusion before 1992 when testing for HCV became available, injection drug use, tattooing by unregulated shops, needle sticks, invasive procedures prior to universal precautions, and also sexual contact. African Americans and Hispanics have higher HCV infection rates than whites.

Spradling and colleagues have demonstrated the low testing rates for HBV and HCV among large cohorts in the U.S. who have private health insurance. Their data substantiate the increased risk for HBV associated with Asian race. They also illustrate the low rate of HBV and HCV testing (14.9%) following determination of an elevated serum ALT, which only increases to 42-44% following a second elevated ALT.

Because more than half of new HBV infections diagnosed in the US were in foreign-born persons, the Centers for Disease Control and Prevention (CDC) expanded testing recommendations for HBV infection in 2008 to include persons born in countries with HBsAg prevalence of ≥2%. Despite this recommendation, and despite the demonstration of cost-effectiveness using 2% prevalence for screening chronic HBV, testing for HBV in the foreign-born has remained inconsistent.[3,4] Many health care providers still lack knowledge about HBV infection, available tests, screening, and vaccination in these high-risk populations.[5-8] The Boston Area Travel Medicine Network (BATMN), a research collaboration of 5 travel clinics in the greater Boston Area, found that only 25% of persons born in countries with HBV prevalence of ≥2% had been tested before their pre-travel consultations.9 An additional 11% of the at-risk travelers tested at the travel clinic visits led to new diagnosis of chronic HBV infection in 3.3%.

Similarly, the CDC has recommended HCV testing for persons with possible exposures since 1998. However, risk-based testing strategy has yielded suboptimal results in identifying HCV-infected persons; a number of studies have found that providers lacked knowledge about HCV prevalence, natural history, diagnostic tests and treatment, and recommendations for testing. Moreover, only 55% of persons with HCV infection reported known exposure risk, and the remaining 45% reported no recognized exposure risk.10 In 2012, CDC also expanded routine screening for HCV infection to include persons born between 1945-1965.[10] The Institute of Medicine has identified deficiencies in knowledge and awareness, surveillance, immunization, and services for viral hepatitis in the US, and recommended strategies to optimize prevention and control of HBV and HCV, policies fully endorsed by the Department of Health and Human Services and CDC.[11] Early diagnosis of chronic HBV and HCV infections can lead to improved therapeutic response, lower viral loads, halt progression to cirrhosis, and prevent hepatocellular carcinoma. Immunization should also be recommended for non-immune persons at risk for HBV exposure, household members and sexual contacts of HBV-infected individuals.

Specialists in fields with expertise in hepatitis and who may evaluate patients for reasons such as international travel — including those in travel and tropical medicine, infectious diseases, and gastroenterology — can reach this broader population that needs to be screened. Through the collaboration of specialists with primary care providers, significantly improvement of screening in high-risk populations is achievable. ■

References

1. Colvin HM, et al. Editors; Committee on the Prevention and Control of Viral Hepatitis Infections; Institute of Medicine. Hepatitis and Liver Cancer: A National Strategy for Prevention and Control of Hepatitis B and C. (Summary available at: http://www.nap.edu/catalog/12793.html. Accessed August 7, 2010.) The National Academies Press, Washington, DC, 2010.
2. Centers for Disease Control and Prevention (CDC). Hepatocellular carcinoma – United States, 2001-2006. *MMWR* 2010;59(17):517-520.
3. Weinbaum CM, et al. Recommendations for identification and public health management of persons with chronic hepatitis B virus infection. *MMWR* 2008; 57(RR-8):1-28.
4. Hutton DW, et al. Cost-effectiveness of screening and vaccinating Asian and Pacific Islander adults for hepatitis B. *Ann Intern Med* 2007;147(7):460-469.
5. CDC. Screening for chronic hepatitis B among Asian/Pacific Islander populations in New York City, 2005. *MMWR* 2006;55(18):505-9.
6. CDC. Characteristics of persons with chronic hepatitis B – San Francisco, California, 2006. *MMWR* 2007; 56(18):446-448.
7. Ferrante JM, et al. Family physicians' knowledge and screening of chronic hepatitis and liver cancer. *Family Med* 2008;40(5):345-351.
8. Dulay M, et al. Are primary care clinicians knowledgeable about screening for chronic hepatitis B infection? Abstracts from the 30th annual meeting of the Society of General Internal Medicine, Toronto, Canada. *J Gen Intern Med* 2007;22(Suppl 1):100.
9. Chen LH, et al. Hepatitis B screening in US travelers seen in the Boston Area Travel Medicine Network. *J Travel Med* 2012, in press.
10. Smith BD, et al. Centers for Disease Control and Prevention.

Recommendations for the identification of chronic hepatitis C virus infection among persons born during 1945-1965. *MMWR* 2012;61(RR-4):1-32.

11. Department of Health and Human Services. Combating the silent epidemic of viral hepatitis: action plan for the prevention, care & treatment of viral hepatitis. Available at: http://www.hhs.gov/ash/initiatives/hepatitis/actionplan_viralhepatitis2011.pdf.

ABSTRACT & COMMENTARY

Meningococcal Vaccine Recommendations for HIV+ Men Who Have Sex with Men

By Mary-Louise Scully M.D.

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

SYNOPSIS: A cluster of cases of invasive meningococcal disease among men who have sex with men (MSM) in New York City since September 1, 2012 prompts expanded recommendations for meningococcal vaccination in HIV-infected MSM patients felt to be at increased risk.

SOURCES: New York City Department of Health and Hygiene. Alert # 28, 2012. Update: Meningococcal Vaccine Recommendations for HIV infected Men Who Have Sex With Men. https://a816-health29ssl.nyc.gov/sites/NYCHAN/WebPages/home.aspx Accessed Nov. 10, 2012.

Massachusetts Department of Public Health. Health Advisory. Meningococcal Vaccine Recommendations for Men Who have Sex With Men, October 25, 2012. http://www.mass.gov/eohhs/docs/dph/cdc/immunization/alerts-meningococcal-msm.pdf Accessed Nov. 10, 2012

There have been 14 cases of invasive Neisseria meningitidis infection among men who have sex with men (MSM) in the New York City (NYC) area since 2010. There was 1 case in 2010, 4 cases in 2011, and now 9 cases in 2012. Nine of 14 total cases were HIV-infected, and 3 of the 4 deaths that occurred were also in HIV-infected patients. Serogroup C Neisseria meningitidis was the predominant serogroup responsible for disease. The median age was 32 with a range from 21-59 years. Six cases lived in Brooklyn, 3 in Manhattan, 2 in the Bronx, 2 in Queens, and one was undomiciled. The estimated annual incidence rate of invasive meningococcal disease (IMD) in MSM is 5.9 per 100,000 compared to a rate in all other New Yorkers of 0.25 per 100,000.

In October, the New York Department of Health and Hygiene issued a recommendation to administer meningococcal vaccination to HIV-infected men who are NYC residents and who had intimate contact with a man met either through an online website, smart phone application, bar, or party since September 1, 2012. On October 25, 2012 the Massachusetts Department of Health followed up with a recommendation to immunize MSM, especially those infected with HIV, if their travel or travel plans included visiting NYC with expected close social interaction with other MSM, or if such social interaction with men from NYC occurs on a regular basis.

■ COMMENTARY

Invasive meningococcal disease (IMD) remains a feared disease both among the lay population and heath care workers, as the disease is known for its rapid progression and high morbidity and mortality if there is a delay in diagnosis and initiation of treatment. IMD can begin with non-specific flu-like symptoms, but can progress quickly to severe headache, stiff neck, photophobia, nausea, vomiting, altered mental status, and sepsis. All ill patients should be closely examined for the presence of a petechial or purpuric rash, which is often present with meningococcemia. However, in the early stages of illness the rash may be maculopapular and blanch. In addition, severe muscle pain, usually in the extremities or back, or severe abdominal pain may be an early clue to the diagnosis.

Three quadrivalent meningococcal vaccines are available in the United States and include protection against the four serogroups of N. meningitidis (A, C, W135, and Y). Serogroup B is not included in any of the vaccines. Serogroups B, C, and Y cause the majority of disease in the United States, whereas serogroup A, C, and W-135 are associated with outbreaks within the classic meningitis belt of sub-Saharan Africa.[1] In patients 55 years of age and younger,

a meningococcal conjugate vaccine (MCV4) should be used. HIV- infected adolescents and HIV-infected patients under age 55 who meet criteria for immunization should receive two doses of MCV4 separated by 8 weeks. For patients 56 years and older polysaccharide vaccine (MPSV4) is the approved vaccine for use and only one dose is needed. However, health care providers have the option to administer MCV4 off-label to older patients with the same 2-dose schedule used in younger patients. Influenza vaccine can be administered at the same time as either MCV4 or MPSV4.
At the present time, meningococcal vaccine is not universally recommended for all HIV-infected patients, though the lesson learned from this outbreak is that MSM and in particular HIV-infected MSM are at higher risk for invasive meningococcal disease and death. So in light of this report, in my own practice I plan to discuss and offer meningococcal vaccination to all my HIV-infected MSM patients since as Ben Franklin once said wisely "an ounce of prevention is worth a pound of cure." ■

References

1. CDC. Meningococcal Disease http://www.cdc.gov/meningococcal/clinical-info.html Accessed November 10, 2012.

Infectious Disease [ALERT]

Updates

By Carol A. Kemper, MD, FACP

Endocarditis of Implanted Valves

Puls M, et al. Infection of percutaneously implanted prosthetic aortic valves. *EuroIntervention* 2012 Sep 27. doi:pii:20120625-03 [Epub ahead of print].

Eisen A, et al. Infective endocarditis in the transcatheter aortic replacement era: comprehensive review of a rare complication. *Clin Cardiol* 2012 Sept 18. doi:10.1002/clc.22052. [Epub ahead of print].

I was recently asked to provide consultation for a 92-year-old woman with an aortic CoreValve who presented with a pacer pocket infection secondary to MRSA. Blood cultures had not been obtained prior to the initiation of antimicrobials but both leads on extraction proved positive for MRSA. Both transthoracic and transesophageal echocardiograms showed no evidence of CoreValve vegetation, although there was a modest paravalvular leak. How to evaluate and treat this woman?

Puls and colleagues evaluated the first 180 consecutive patients to undergo TAVR at their institution, finding a one-year incidence of TAVR endocarditis of 3.4% based on Duke criteria. This figure may be inflated, as the Duke criteria include paravalvular leaks. However, paravalvular regurgitation is quite common with TAVR, and moderate to severe "leaks" are reported in 7% to 20% of patients. Based on a search of the literature, the incidence of endocarditis involving percutaneously implantable valve devices may vary from as little as 0% to up to 2.3%, with varying durations of follow-up. Eisen and colleagues reported 10 cases, six involving CoreValves and 4 involving SAPIEN valves. Infections were due to *Staphylococcus lugdenensis* (n = 2), enterococcus (n = 2), and *candida albicans* (n = 2), as well as *S epidermis, Streptococcus angiosus, Moraxella nonliquefaciens, corynebacterium,* and *Histoplasma capsulatum*. Four of the 10 patients died, all within 14-54 days. Two patients required surgical valve replacement.

Suspicion for infection of percutaneously implantable prosthetic aortic valves should remain high in the appropriate clinical circumstances, similar to that for surgically implanted prosthetic valves, although the usual echocardiographic features may be misleading. ■

Pumas with Lyme?

Girard YA, et al. Zoonotic vector-born bacterial pathogens in California Mountain Lions (Puma concolor), 1987-2010. *Vector Borne Zoonotic Dis* 2012;(11):913-921.

Active infectious disease surveillance of the California Mountain Lion population yields some interesting results, in terms of diseases that also affect humans. Sera was obtained from 442 Mountain Lions throughout California from 1987-2010, 70% of which were killed on depredation permits (meaning they were exhibiting predatory habits proximate to residential communities or livestock

areas). Antibody studies demonstrated that exposure to Bartonella henselae and Borrelia burgdorferi were quite common, found in 37.1% and 19.9% of animals tested, respectively. *B henselae* DNA extracted from samples was similar to common strains of this organism found in domestic cats and humans.

Antibodies to Yersinia pestis were observed in 7 (1.4%) animals, all of which were female, and found on the Eastern and Western Sierra Nevadas. And, antibody evidence of exposure to *Francisella tularensis* (1.4%) and *Anaplasma phagocytophilum* (5.9%) was less common.

The high rate of exposure to lyme disease may not be surprising, as deer are a dietary staple for Mountain Lions – but one wonders if they ever develop symptomatic disease. Humans are at little risk for acquiring zoonotic infections from Mountain Lions, even if you could get that close. But game wardens and rescue centers should be cognizant of these possibilities. ■

The Smell of *C Difficile*

Rao, K, et al. The Nose knows not: poor predictive value of stool sample odor for detection of *Clostridium difficile*. *Clin Infect Dis* 2012;Nov. 19. Epub ahead of print).

Ever walked by a patient room and thought – ahah! *C. diff* ? It is theoretically possible to detect the presence of *C. difficile* enterocolitis (CDI) based on the odor. Unique volatile organic compounds may be detected in the stools of patients with CDI. Gas chromatography can effectively distinguish 100% of the time between the stools of CDI patients and those with ulcerative colitis or other gastroenteritis. But can medical staff do the same? And could a protocol for contact isolation be built around this observation ?

These authors recruited 18 nursing staff from hospital wards, and presented them with 10 blinded stool samples. Five samples were positive for CDI and 5 were negative based on PCR and toxin immunoassay results. The nurses varied in experience from 1 to 30 years with 8 of the 18 having more than 10 years of experience.

After sniffing and scoring each sample, 61% expressed confidence in their guesses. The median percent correct was 45%. Positive specimens were more likely to be scored incorrectly than negative ones (69% vs 26%, respectively, p = .01). Those with confidence in their sniffing abilities and / or more experience were no more likely to be correct than those with less confidence or less experience. In fact, the authors state that no single sniffer did better than random chance.

I am not convinced by this study — blinded or not — and still confident of my sniffing abilities! One wonders if the volatile components given off by the collected specimens had waned sufficiently by the time the nurses were gathered together for the study. Perhaps there is something about the smell of a freshly passed stool by a patient lying in bed, than in a cup in the lab. ■

STD Screening of the Adult Film Industry

Rodriquez-Hart C, et al. Sexually transmitted infection testing of adult film performers: Is disease being missed? *Sex Transm Dis* 2012;(39(12):989-994.

Active STD surveillance of the adult film industry in many parts of the United States is a requirement. It might seem odd that the bureaucrats of Cal-OSHA are responsible for establishing the rules regulating the sex film industry, but when sex becomes work, risk becomes subject to regulation. The State of California requires any adult film worker to be screened and certified STD-free, based on blood and urine testing, within 30 days of performance. However, even regular monthly STD screening is fallible, as demonstrated by the transmission of HIV among adult film workers in 2004, from a man who fell into the classical "window" period with previously negative monthly serological screening specimens. Over the next month, three of his 13 female film partners converted their HIV tests, after having been screened negative in the preceding month.[1]

This study suggests that current screening methods could be expanded. Between May and September 2010, 168 adult film workers were offered more expanded STD screening with GC and chlamydia testing of oropharyngeal, rectal and urogenital specimens. Two-thirds of the participants were female. Not surprisingly, gonorrhea and chlamydia infections involving the rectum and the oropharynx would have been missed based on current urine screening methods. But the frequency of these infections was surprising. Forty-seven persons (28%) tested

positive for GC and/or chlamydia, nearly one-fourth of which would have been missed based on current screening requirements. Gonorrhea was predominant, resulting in 37 oropharyngeal infections and 23 rectal infections, 95% and 91% of which, respectively, were asymptomatic.

The nature of the adult film business results in frequent exposure to multiple sex partners – with varying sites of anatomic involvement. For this reason, it makes sense to expand STD screening to those other sites (oropharyngeal and rectal), irrespective of symptoms. Adult film workers should be aware that STD screening is not a guarantor of disease-free status, and there are inherent risks to their job. Caution outside the work place, with strict adherence to safe sex practices and condom use, would improve the risks in the work place.

1. CDC. HIV transmission in the Adult Film Industry – Los Angeles, California, 2004; *MMWR* 2005;54(37):923-926. ■

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. Sequencing of a new human coronavirus identified a novel betacoronavirus most closely related to which animal?

A. civet cats
B. ferrets
C. chickens
D. bats

2. Chronic hepatitis B and chronic hepatitis C infections:

A. Can usually be detected by review of exposure risks

B. Are uniformly screened for in persons with private health insurance

C. Have newer antiviral therapies that can lead to sustained viral response

D. Occur rarely in Western developed countries such as the US

3. Which of the following statements are true about invasive meningococcal disease (IMD) and its prevention?

A. Serogroup B can be prevented with vaccination

B. Meningococcal vaccination is contraindicated at ages over 65

C. The annual incidence rate of IMD in MSM in New York City exceeds that of the general population.

D. Meningococcal vaccine should not be co-administered with influenza vaccine.

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]

Association between timing of antibiotic administration and mortality from septic shock in patients treated with a quantitative resuscitation protocol

Rate of transmission of extended-spectrum Beta-lactamase-producing enterobacteriaceae without contact isolation

Safety and Effectiveness of meropenem in infants with suspected or complicated intra-abdominal infections

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.*

Zolpidem and Risk of Falls in Hospitalized Patients

In this issue: Zolpidem and risk of falls; AVR and anticoagulation; statins in cancer patients; and FDA actions.

Zolpidem and risk of falls

Zolpidem (Ambien) increases the risk of falls in inpatients, according to a new study from the Mayo Clinic. The records of hospitalized patients who were not in the intensive care unit were reviewed in this retrospective cohort study. The rate of falls was compared in those who were administered zolpidem vs those for whom it was prescribed but not administered. After controlling for age, gender, insomnia, delirium, dose of zolpidem, Charlson comorbidity index, Hendrich's fall risk score, length of stay, visual impairment, gait abnormality, dementia/cognitive impairment, and concomitantly administered meds, the rate of falls was four times higher in those administered zolpidem (n = 4962) vs those who were prescribed but did not receive zolpidem (adjusted odds ratio 4.37, 95% confidence interval [CI], 3.34-5.76; $P < 0.001$). The authors conclude that zolpidem was a strong, independent, and potentially modifiable risk factor for inpatient falls. The authors suggest that changing order sets so that zolpidem use is not encouraged could potentially reduce fall rates in hospitalized patients. They also suggest that there is limited evidence to recommend other hypnotic agents as safer alternatives (*J Hosp Med* published online Nov. 19, 2012. doi: 10.1002/jhm.1985). ■

Anticoagulation and AVR

Bioprosthetic valves are preferred to mechanical valves for aortic valve replacement (AVR) in the elderly because of lack of need for anticoagulation in the long-term, but short-term anticoagulation is required. The duration of anticoagulation after valve replacement has been unclear. Now, a new study from Denmark suggests 6 months is optimal. Using the Danish National Patient Registry, more than 4000 patients who had a bioprosthetic AVR between 1997 and 2009 were identified. Rates of stroke, thromboembolic events, cardiovascular death, and bleeding were assessed along with warfarin treatment duration. Rates of events per 100 person-years in patients not treated vs those treated with warfarin for 3 months were 7 vs 2.7 for stroke, 13 vs 4 for thromboembolic events, 11.7 vs 5.4 for bleeding, and 32 vs 3.8 for cardiovascular death. The rate of cardiovascular death was 6.5 vs 2.0, favoring warfarin from 90 days to 179 days. The authors conclude that stopping warfarin within 6 months of bioprosthetic AVR surgery was associated with increased cardiovascular death. These findings challenge the current guidelines that recommend 3 months of antithrombotic treatment after AVR surgery suggesting that "patients will gain from an additional 3 months of warfarin treatment in terms of reduced cardiovascular death without risking significant increase in bleeding events" (*JAMA* 2012;308:2118-2125). An accompanying editorial states that this study provides important information to help clinicians understand the benefits and risks of warfarin use after bioprosthetic aortic valve implantation, but it

This supplement was written by William T. Elliott, MD, FACP, Chair, Formulary Committee, Kaiser Permanente, California Division; Assistant Clinical Professor of Medicine, University of California-San Francisco. In order to reveal any potential bias in this publication, we disclose that Dr. Elliott reports no consultant, stockholder, speaker's bureau, research, or other financial relationships with companies having ties to this field of study. Questions and comments, call: (404) 262-5404. E-mail: neill.kimball@ahcmedia.com.

does not address the issue of adjunctive aspirin or the role of new novel oral anticoagulants (*JAMA* 2012;308:2147-2148). ■

Statins in patients with cancer

Patients taking a statin when diagnosed with cancer have a better prognosis than patients who are not taking statins, according to a new study. This study also used the Danish Registry in which all patients with a cancer diagnosis between 1995 and 2007 were evaluated. Roughly 19,000 patients were on a statin prior to diagnosis and 277,000 were not. Those taking statins were 15% less likely to die of any cause and 15% less likely to die of cancer (hazard ratio 0.85, 95% CI, 0.82-0.87 for cancer). The benefit was present regardless of statin dose or cancer type. The authors suggest that this is biologically plausible since cholesterol is needed for cell proliferation. They suggest "a need for trials of statins in patients with cancer" (*N Engl J Med* 2012;367:1792-1802). Previous studies have suggested reduced cancer mortality with statins in patients with prostate cancer and reduced recurrence rates in breast cancer patients. ■

FDA actions

The FDA has concluded a safety review of dabigatran (Pradaxa) and found that the drug is not associated with more serious bleeding events than warfarin. The review was done using insurance claims and data from the FDA's Sentinel Initiative. According to the FDA, the bleeding rates are consistent with the observations from large clinical trials, including RE-LY, which showed that bleeding rates in patients newly started on dabigatran were similar to rates associated with new use of warfarin. Therefore, the FDA has not changed its recommendation regarding dabigatran (FDA Drug Safety Communication, Nov. 2, 2012). The next day, *The New York Times* published an article reporting that dabigatran has been associated with more than 500 deaths in the United States since it was introduced. It also detailed several tragic cases of bleeding deaths associated with the drug. The article indicts the FDA stating "… the approval process was not sufficiently rigorous because it allowed a potentially dangerous drug to be sold without an option for reversing its effects." The article also mentions more than 100 lawsuits that have been filed in federal courts "…and thousands more are expected" (*The New York Times* Nov. 3, 2012:B1).

The FDA has expanded the approval of rivaroxaban (Xarelto) to include treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), both for acute treatment and prevention of recurrence. The drug is already approved for prevention of DVT and PE after knee and hip replacement surgery and for prevention of stroke in patients with non-valvular atrial fibrillation. It is the first oral drug approved to treat DVT and PE since warfarin was approved 60 years ago; but unlike warfarin, rivaroxaban can be used as monotherapy from diagnosis until treatment is discontinued. Approval was based on three studies of nearly 9500 patients with DVT or PE randomized to rivaroxaban, enoxaparin/vitamin K antagonist, or placebo. Rivaroxaban was equivalent to enoxaparin/vitamin K antagonist and superior to placebo for preventing recurrent DVT or PE.

The FDA has approved a new egg-free flu vaccine for adults. The vaccine is manufactured using cultured mammalian cells instead of fertilized chicken eggs. The manufacturer claims that the cell culture technology enables a rapid response to public health needs, such as a pandemic, since cell culture technology allows vaccines to be manufactured within weeks as opposed to traditional flu vaccines that depend on a large number of fertilized chicken eggs to grow the virus. Cell culture technology is used for several other vaccines including polio, rubella, and hepatitis A vaccines. Approval was based on a randomized, controlled clinical study of 7700 adults ages 18-49. The new vaccine was 83.8% effective in preventing influenza when compared to placebo. Injection site reactions are the most common side effects. The new vaccine is marketed as Flucelvax by Novartis.

The FDA has approved the first Janus kinase (JAK) inhibitor for the treatment of rheumatoid arthritis (RA). Tofacitinib, dosed orally twice a day, is approved for RA patients who have failed methotrexate. The drug will compete with the parenteral RA drugs adalimumab (Humira), etanercept (Enbrel), and infliximab (Remicade). Tofacitinib carries a boxed warning regarding the increased risk of opportunistic infections, tuberculosis, cancers, and lymphoma; increases in cholesterol and liver enzymes; and decreases in blood counts. Approval was based on seven clinical trials in which the drug showed improvements in clinical response and physical function compared to placebo in patients with moderate-to-severe RA. Tofacitinib will be marketed by Pfizer as Xeljanz. The cost is projected to be just over $2000 per month, similar to other non-methotrexate biologic treatment options. ■

Infectious Disease [ALERT]

2012 Index