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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

Surgeon-To-Patient HBV Transmission, CDC Update on Chronically Infected

By Stan Deresinski, MD, FACP, FIDSA

Clinical Professor of Medicine, Stanford University, Hospital Epidemiologist, Sequoia Hospital, Redwood City, CA, is Editor for Infectious Disease Alert.

SOURCE: Enfield KB, et al. Transmission of hepatitis B virus from an orthopedic surgeon with a high viral load. *Clin Infect Dis* 2013;56:218-24.

A surgeon reported having suffered a sharps injury while performing an orthopedic procedure. Baseline testing found no evidence of HBV infection in the source patient, but determined that the surgeon had preexisting HBV infection, with positive HBsAg, positive HBeAg, negative IgM anti-HBc, and normal serum hepatic transaminases. The surgeon had emigrated from a country with a high prevalence of HBV infection, had completed his residency training in the U.S., and had been employed at a different hospital prior to his current place of practice. He had previously received 2 complete courses of HBV vaccination without developing a protective level of anti-HBs. However, no additional testing of HBV markers had been performed at that time.

Because his serum HBV DNA concentration was >17.9 million IU/mL, he was removed from surgical practice. Former patients of the surgeon at his previous facility were evaluated for evidence of HBV infection. Of the 232 patients who consented to testing, 2 had acute HBV infection and their virus had >99.9% nucleotide identity with that of the surgeon. There were an additional 6 patients who had evidence of past HBV exposure without other identified risk factors, suggesting possible transmission from the surgeon. Two patients had evidence of past

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Infectious Disease [ALERT]

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HBV exposure but had risk factors; transmission from the surgeon was considered indeterminate in these cases. The surgeon was considered to be technically proficient and no breaches in procedure were retrospectively identified.

■ COMMENTARY

It is useful to examine the management of the surgeon described by Enfield and colleagues relative to current guidelines.[1,2] The Centers for Disease Control and Prevention now recommends that providers and students at increased risk for HBV infection, such as, in this case, those born to mothers in or from endemic countries, should undergo prevaccination testing. Prevaccination testing for chronic HBV infection should also be performed on all providers performing exposure-prone procedures. Health-care providers who do not have a protective concentration of anti-HBs (>10 mIU/ml) after revaccination (i.e., after receiving a total of 6 doses) should be tested for HBsAg and anti-HBc to determine their infection status. This was not done with the surgeon described.

HBV infection in health-care providers and students who do not perform invasive exposure-prone procedures should be managed as a personal health issue and does not require special oversight. In contrast, chronically infected surgeons and others who perform exposure-prone Category I activities should undergo oversight by an Expert Panel. CDC has defined 2 categories of exposure-prone patient care procedures (confusingly, SHEA has 3 categories, with a reverse order of risk and with an intermediate Category II defined as one in which procedures for which transmission is theoretically possible but unlikely):

Category I. Procedures known or likely to pose an increased risk of percutaneous injury to a health-care provider that have resulted in provider-to-patient transmission of HBV. These procedures are limited to major abdominal, cardiothoracic, and orthopedic surgery, repair of major traumatic injuries, abdominal and vaginal hysterectomy, caesarean section, vaginal deliveries, and major oral or maxillofacial surgery (e.g., fracture reductions). Techniques that have been demonstrated to increase the risk for health-care provider percutaneous injury and provider-to-patient blood exposure include:
• digital palpation of a needle tip in a body cavity and/or
• the simultaneous presence of a health care provider's fingers and a needle or other sharp instrument or object (e.g., bone spicule) in a poorly visualized or highly confined anatomic site.

Category II. All other invasive and noninvasive procedures.

CDC recommends that HBV infection alone should not disqualify infected individuals from the study or practice of surgery, dentistry, medicine, or allied health fields, but strongly emphasizes the need for strict adherence to standard precautions. They also recommend against a variety of potentially onerous monitoring and management requirements as well as constraints on practice. Chronically infected surgeons and others who perform Category I activities may conduct such procedures if low or undetectable HBV viral load is documented at least every 6 months, or more frequently as indicated by such factors as a change in antiviral therapy. A threshold viral load level of 1000 IU/ml (5000 genome equivalents/ml) is recommended, as is an assay with a lower limit of detection of 10-30 IU/ml. Fluctuations above the threshold will necessitate that the provider abstain from performing exposure-prone procedures while subsequent retesting occurs, and if needed,

modifications or additions to the health-care provider's drug therapy and other reasonable steps are taken.

Finally, the Consult Subcommittee of CDC's Public Health Ethics Committee has noted that providers have an ethical and professional obligation to know their HBV status and to act on such knowledge accordingly.

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ABSTRACT & COMMENTARY

Meningoencephalitis due to *Borrelia miyamotoi*

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: An 80 year old woman from New Jersey with a past history of non-Hodgkin's lymphoma presented with progressive confusion over 4 months. Spirochetes were detected in CSF by light microscopy and the presence of *B. miyamotoi* was confirmed by PCR. The patient initially received ceftriaxone and subsequently completed a 30-day course of IV penicillin G and recovered.

SOURCE: Gugliotta JL, et al. Meningoencephalitis from *Borrelia miyamotoi* in an immunocompromised host. *New Eng Jrl Med* 2013;368:240-5.

An 80-year-old woman with a past history of non-Hodgkin's lymphoma (follicular type, stage IIA) developed progressive confusion, unsteady gait, difficulty hearing and weight loss over a 4 month period. (She had initial treatment of her lymphoma with CAVP-rituximab in 2005 followed by rituximab every 6 months until several months prior to onset of her symptoms in 2012.) She lived on a farm in New Jersey and spent time outside but reported no known tick exposures, although she developed erythema migrans in 2007 and received a 2 week course of doxycycline with complete resolution of her symptoms at that time. MRI of the brain performed in early 2012 4 months after onset of neurologic symptoms was unremarkable. Lumbar puncture showed 65 WBC/mm3 (23% pmn, 70% lymphocytes, 6% monocytes, and 1% uncharacterized cells), protein > 300 mg/dL and glucose 33 mg/dL. Giemsa stain of CSF revealed spirochetes. The patient experienced chills, fever and mild hypotension 9 hours after receiving her initial dose of cetriaxone, consistent with a Jarisch-Herxheimer reaction. PCNG 24 million units IV daily was initiated and her mental status improved dramatically over the initial 5 days of treatment. After approximately 4 weeks of antimicrobial treatment the CSF WBC had decreased to 21 cells/mm3, protein had decreased to 168 mg/dL, and glucose had increased to 41 mg/dL. Organisms were no longer seen.

Spirochetes seen in the initial specimen of CSF failed to grow in culture. EIA of CSF for *B. burgdorferi* antigen was negative and antibodies to *B. burgdorferi* were negative on both serum and CSF. Immunoblot analyses were also negative. Real-time PCR showed amplification of a *Borrelia* species but primers to amplify OspA gene were negative, ruling out *B. burgdorferi*. Sequencing and phylogenetic analysis of 16S rRNA and flagellin genes were consistent with B. miyamotoi-like spirochetes.

■ COMMENTARY

The genus borrelia can be divided into two taxonomic groups: basically Lyme disease and relapsing fever. Of the relapsing fever group, *B. recurrentis* (louse-borne), *B. hermsii*

(Ornithodos ticks), *B. lonestari* (Amblyomma ticks), *B. theileri* (Boophilus ticks), and *B. miyamotoi* (transmitted by Ixodes ticks in North America and Haemophysalis ticks in Japan) have been identified. Rare human cases of *B. miyamotoi* infections have been described in Russia (mainly in patients presenting with nonspecific fever), but it is possible that cases are under-reported since this organism is commonly present in Ixodid ticks world-wide. Studies in residents of New England demonstrate antibody reactivity to this organism may be present in up to 3% of individuals. It is likely that *B. miyamotoi* may be a cause of "idiopathic meningoencephalitis" in both immunocompetent and immunocompromised patients. A recurrent theme of the 37 years I have spent since medical school is "hold on to your hat—here's another new disease!" ■

ABSTRACT & COMMENTARY

Delayed Primary Epstein-Barr Virus Infection: Clinical and Immunologic Manifestations

By Richard R. Watkins, MD, MS, FACP

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

SYNOPSIS: A prospective study on Epstein-Barr virus seronegative college freshmen found that primary infection was symptomatic in 89% of cases. Kissing was the primary risk factor for infection, and blood viral load, CD8+ lymphocytosis, and IL-6 levels correlated with disease severity.

SOURCE: Balfour HH, et al. Behavior, Virologic, and Immunologic Factors Associated with Acquisition and Severity of Primary Epstein-Barr Virus Infection in University Students. *J Infect* 2013;207:80-88.

In the United States, approximately 50% of individuals develop antibodies to Epstein-Barr virus (EBV) by age 5. Infections during the first decade are usually asymptomatic, while disease is most commonly diagnosed in adolescents of higher socioeconomic status. Researchers at the University of Minnesota sought to determine the proportion of delayed primary infections that are symptomatic. Another goal was to investigate how CD8+ lymphocytosis correlated with symptomatic disease.

Two freshman classes were followed prospectively throughout their undergraduate years. Of 202 EBV antibody-negative students, 143 (71%) were enrolled in the surveillance phase. They were seen every 8 weeks while in school and during breaks if they remained in the area. The visits involved obtaining a medical history, an oral wash specimen, a 40 mL venous blood sample, and completion of a health questionnaire. Sera collected were tested for EBV antibodies. Subjects who developed signs and symptoms suggestive of acute EBV infection were seen as soon as possible and study specimens and questionnaires were obtained. Primary EBV infection was defined as a positive result of an EBV antibody test and the presence of EBV DNA in the oral and/or blood compartment of a subject who was previously negative for both EBV antibodies and EBV DNA. Primary EBV infection was classified clinically as infectious mononucleosis (with at least two of the following: sore throat, cervical lymphadenopathy, fever, and fatigue), symptomatic (symptoms present but did not fulfill the definition of infectious mononucleosis), or asymptomatic. Severity of illness was graded from 0 (asymptomatic) to 6 (essentially bedridden).

Sixty-six out of 143 students developed primary EBV infection during the four years of observation. The incidence of infection during the freshman year (26 cases per 100 person-years) was more than twice the mean incidence during the following three years (10 cases per 100 person years; P = .002). The incidence was greater in women than men (23.6 vs. 16.1 cases/person-year) but was not statisically significant. Sexual behavior was a risk factor for primary EBV infection, with students reporting deep kissing with or without coitus having similar distributions of time to infection. Infectious

mononucleosis developed in 51 subjects (77%). It was symptomatic but not meeting the definition of mononucleosis in 8 subjects (12%), and 7 asymptomatic (11%). EBV DNAemia was documented in 42 subjects (64%). Heterophile antibodies were documented in 50 (77%) of 65 subjects, IgM antibodies in 54 (83%) of 65 subjects, and IgM antibodies were found as early as 8 days before symptoms began and persisted as long as 420 days after symptom onset.

The authors quantified CD8+ T-cell numbers and activation over time. CD8+ T-cell numbers increased the most during the first 2 weeks following symptom onset. They also observed an upregulation of CD38, HLA-DR, and granzyme B on total CD8+ T-cells in the first two weeks. Moreover, the investigators discovered an expansion of NK cells in the blood during acute disease correlated with CD8+ T-cell numbers. Severity of disease corresponded with the quantity of EBV in whole blood, CD8+ T-cell numbers and granzyme B expression. Of several cytokines evaluated during acute infection (including interferon γ), only IL-6 correlated significantly with severity of disease.

COMMENTARY

As mentioned in an accompanying commentary, what sets this study apart from others on primary EBV infection is the rigor of the prospective follow-up.[1] The investigators should be commended for a study design that involved 143 participants who gave oral and blood samples every 8 weeks over a period of 4 years, and donated additional samples whenever they developed a febrile illness. Sixty-six of them acquired primary EBV infection, of which 89% were symptomatic. This result is much greater than the approximately 25%-50% incidence of symptomatic primary EBV infection reported in prior studies. Thus, it seems likely the results of the present study reflect the true incidence of symptoms of primary infection in this age group. Deep kissing was identified as the main risk factor for EBV acquisition, as students who engaged in this activity had similar conversion rates whether or not they engaged in sexual intercourse, and those with no history of kissing remained seronegative.

A prior study found that NK cell numbers correlated with less severe illness, not more as the present study reported.[2] This discrepancy could be due to the smaller numbers of patients in the older study, which lacked internal controls for NK cell numbers and frequency before, during, and after primary EBV infection. Furthermore, data from the current report suggest that both NK cells and CD8+ T-cells respond similarly to the intensity of viral challenge. It is possible that a particular subset of NK cells is responsible for better viral control and symptom reduction, and further research on this topic seems warranted. Indeed, future prospects for an EBV vaccine hinge on our continued elucidation of these complex host-virus interactions.

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2. Williams H, et al. The immune response to primary EBV infection: a role for natural killer cells. *Br J Haematol* 2005; 129:266-274. ■

ABSTRACT & COMMENTARY

Pediatric Tuberculosis in the United States

By Hal B. Jenson, MD, FAAP

Dean, Western Michigan University School of Medicine, Kalamazoo, MI.

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

SYNOPSIS: Three-fourths of US-born children with tuberculosis have lived in other countries (>2 months) or have an international connection in the immediate family, including 66% having at least one parent born outside of the US.

SOURCE: Winston CA, et al. Pediatric and adolescent tuberculosis in the United States, 2008-2010. *Pediatrics* 2012;130:e1425-e1673.

An analysis was performed of incident cases of tuberculosis in the United States reported to the Centers for Disease Control and Prevention from 2008-2010. Beginning in 2009, data are now reported with additional epidemiologic information that helps identify

links to another verified case of tuberculosis. Cases were epidemiologically linked by matching *Mycobacterium tuberculosis* genotypes based on spoligotype and 12-locus mycobacterial interspersed repetitive units, which are used routinely in national tuberculosis surveillance and have >95% discriminatory power.

Children and adolescents comprised 7% of all cases of tuberculosis reported in the US, with 977 cases in 2008, 865 in 2009 and 818 in 2010.

During 2008-2010, 822 (31%) were among foreign-born persons (not US citizens at birth) and 1826 (69%) were among US-born persons. For most (95%) foreign-born persons, the only country in which they had lived outside the United States was their country of birth. Foreign-born persons were older (11.0 years versus 5.5 years, P<0.0001) and more likely to have pulmonary disease (72% versus 67%). US-born persons were more likely to have extrapulmonary or combined pulmonary and extrapulmonary disease. Among persons with known HIV status, 1% of both US- and foreign-born persons were HIV-positive (P=0.58).
More than half (52%) of the US-born persons were Hispanic, compared with 30% of foreign-born persons. Among US-born persons, countries of birth for parents included the United States (35%), Mexico (29%), Guatemala (5%), India (4%), Vietnam (3%), El Salvador (3%), and Honduras (3%). Among foreign-born persons, countries of birth for parents included the United States (15%), Mexico (12%), the Philippines (10%), Burma (8%), Haiti (7%), and Somalia (6%). Most persons had at least one foreign-born parent, including 85% (169 of 198) of foreign-born persons and 66% (400 of 607) of US-born persons. Among US-born persons with only US-born parents, 43% were African-American.

Of 1680 persons less than 18 years of age with tuberculosis in 2009-2010, 201 (12%) were epidemiologically linked to at least one other person with tuberculosis in the US National Tuberculosis Surveillance database. Among the 188 US-born persons with epidemiologic links, 103 (55%) were linked to a foreign-born case. Among these US-born persons, 70% were initially evaluated for tuberculosis because there were contacts of a known case, with only 16% who sought medical attention because they were symptomatic. Among the 13 foreign-born persons with epidemiologic links, two (15%) were linked to a US-born case. All 13 foreign-born persons were evaluated for tuberculosis because they were contacts of a known case.

More than 96% of culture-positive persons had initial drug susceptibility testing results, with higher proportions of isoniazid resistance (11% versus 6%) and multidrug resistance (4% versus 1%) among foreign-born persons compared to US-born persons.

■ COMMENTARY

This comprehensive nationwide survey of tuberculosis in children and adolescents in the United States underscores the impact of global tuberculosis on disease in the United States. Traditionally, African Americans born in the US are recognized as being at risk for tuberculosis, having eight times the rate of tuberculosis disease as white persons and being more likely to be latently infected with tuberculosis. This study identifies three additional groups of children and adolescents with an increased burden of tuberculosis: 1) US-born children with foreign-born parents; 2) foreign-born children with US-born parents; and 3) foreign-born adolescents. Healthcare providers should document the travel and living history, and clearly identify the country of birth of both the parents and the child when assessing tuberculosis risk in children. Three-fourths of US-born children with tuberculosis have lived in other countries (>2 months) or have an international connection in the immediate family, including 66% having at least one parent born outside of the US, compared with 18% for the general US-born pediatric population. The majority of foreign-born parents were from Mexico or Central America, where the prevalence of tuberculosis is higher. Non-Hispanic Asian and African American persons were also disproportionately represented among foreign-born persons and parents. Only 4% of persons were foreign-born with only US-born parents, which may reflect international adoption.

Foreign-born children should be evaluated for tuberculosis preferably before leaving their home country and again upon arrival in the United States. Testing is uncommon before immigration but recent modifications to US immigration guidelines now stipulate tuberculin skin testing for children 2-14

years of age, a group that previously was not often screened. Immigrant children who are negative for tuberculosis infection should be re-examined within six months of arrival in the United States and after any potential exposure to tuberculosis. Hence, entry into the US health care system is important for recent immigrants, which is frequently challenging.

The majority of foreign-born adolescents with tuberculosis were diagnosed after many years of residence in the United States. Healthcare providers should continue to monitor foreign-born adolescents for tuberculosis and not assume that latent tuberculosis infection was fully treated.

Drug resistance of M. tuberculosis remains a serious concern. Foreign-born children with foreign-born parents showed 18% prevalence of isoniazid resistance and 8% of multidrug resistance, compared to resistance of 6% and 0.4%, respectively, for all US-born cases. Drug susceptibility testing is imperative to guide tuberculosis prophylaxis and treatment regimens. ■

ABSTRACT & COMMENTARY

Tetracycline Treatment of Mycoplasma Infections in Children

By Dean L. Winslow, MD, FACP, FIDSA

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Dr. Winslow is a consultant for Siemens Diagnostic

SYNOPSIS: 258 Japanese children were diagnosed with *M. pneumoniae*-associated pneumonia during 2011. Of the 202 isolates obtained from cultures of NP swabs 87% were shown to be macrolide-resistant. Minocycline (MIN) or doxycycline (DOX) appeared to be more effective than tosufloxacin (TFX) when used for treatment in these patients.

SOURCE: Okada T, et al. Rapid effectiveness of minocycline or doxycycline against macrolide-resistant *Mycoplasma pneumoniae* infection in a 2011 outbreak among Japanese children. *CID* 2012;55:1642-9.

A large outbreak of community acquired pneumonia due to macrolide-resistant *M. pneumoniae* (MRMP) occurred in Japan in 2011 and mainly affected school-age children. 258 of these cases (diagnosed by chest radiography, real-time PCR and antibody titers) were extensively studied. Of the RT-PCR positive nasopharyngeal samples, Mycoplasma was isolated in liquid culture in 202 cases. Antimicrobial susceptibility testing was done by broth microdilution and the 23S ribosomal RNA gene was sequenced. 26 isolates were shown to be macrolide-susceptible and 176 were macrolide-resistant. Of the patients infected with macrolide-resistant isolates, 79% were treated with MIN or DOX and 9% were treated with TFX. 31% of patients treated with macrolides defervesced within 24 hours of initiation of treatment, whereas 58% of patients treated with MIN, 81% of patients treated with DOX and only 31% of patients treated with TFX became afebrile within 24 hours. In a small subset of patients studied with serial quantitative RT-PCR both MIN and DOX were significantly more effective than TFX in decreasing numbers of *M. pneumoniae* DNA copies by 3 days after initiation of treatment.

■ COMMENTARY

M. pneumoniae is an important cause of community-acquired pneumonia (CAP) in both children and adults and may account for 15-30% of hospitalizations for CAP in children.[1] While Mycoplasma is commonly thought to cause mainly a mild "walking pneumonia," the fact is that severe and fatal cases of pneumonia due to Mycoplasma are often seen and in many cases result from the expression of a recently-described novel community-acquired respiratory distress syndrome (CARDS) toxin which can cause a

picture consistent with bronchiolitis obliterans with organizing pneumonia (BOOP).[2,3] Of great concern is the fact that macrolide resistance in Mycoplasma is now present world-wide with as high as 90% prevalence of MRMP in China and Japan,4 and about 8% in the U.S. with some areas of the U.S. showing higher rates.[5] While the study reported here is rather small and retrospective it suggests that MIN and DOX are safe and effective in children with MRMP infections and probably superior to fluoroquinolones in vivo despite similar in vitro activity. Tetracyclines are generally not given to children less than 7 years of age due to the concern for these agents causing staining of permanent teeth. However most of the dental staining seen in children treated with tetracyclines during the 1950's and early 1960's was a result of the use of older tetracyclines, not newer tetracyclines such as MIN or DOX. The degree of teeth discoloration seen with tetracyclines is felt to be a function of these compounds acting as chelating agents binding to divalent cations (Calcium and Magnesium) and MIN and DOX are both relatively weak chelating agents compared to the older drugs. Due to the increasing incidence of severe infections due to MRMP expect to see more frequent and appropriate use of the newer tetracyclines in children in the future.

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5. Yamada M, et al. Rising rates of macrolide-resistant *Mycoplasma pneumoniae* in the central United States. *Ped Infect Dis Journal* 2012: 31: 409-11. ■

FDA APPROVALS

FluBlok – The First FDA-Approved Recombinant Seasonal Influenza Vaccine

On November 20, 2012, Novartis announced that the U.S. FDA had approved Flucelvax, the first cell culture-derived seasonal influenza vaccine for use in individuals >18 years of age. Flucelvax was produced by culture of virus in cell culture, making it the first approved influenza vaccine not grown in embryonated hen's eggs. In the production process, whole virions are harvested, inactivate, and disrupted by detergent, followed by antigen extraction. Protein Sciences have taken influenza vaccine technology a step further.

On January 17, 2003, the FDA approved FluBlok for individuals 18 – 49 years of age, making it the 11th influenza vaccine registered in the U.S. FluBlok is manufactured using a baculovirus expression vector system in insect cell culture (Sf9 cells of the fall armyworm, *Spodoptera frugiperda*). The ability to produce vaccine product in approximately 2 months makes it better suited to deal with influenza virus evolution necessitating yearly reassessment of the vaccine composition. The vaccine contains no adjuvant but does contain approximately 3 times the amount of hemagglutinin antigen present in traditional egg-based vaccines (135 mcg per 3-component dose). Despite significant mismatch between vaccine antigens and circulating viruses, clinical trials demonstrated that FluBlok was 44.6% (95% CI, 18.8%, 62.6%) effective in preventing culture-confirmed influenza meeting the CDC case definition of influenza-like illness.[2]

While the approval of an influenza vaccine utilizing recombinant technology is a significant advance, the need to change the vaccine in response to changes in circulating influenza types is still present. We continue to await the goal of a universal influenza vaccine that provides protection without regard to changes in viral surface antigen.

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1. http://tisvaccines.com/downloads/flucelvax/GLOBAL_Press_Release.pdf
2. Treanor JJ, et al. Protective efficacy of a trivalent recombinant hemagglutinin protein vaccine (FluBlok®) against influenza in healthy adults: a randomized, placebo-controlled trial. *Vaccine* 2011; 29:7733-9. ■

Rapid Identification of Gastro Pathogens Directly from Stool

On January 14, 2013, that the U.S. FDA approved a device allowing detection of multiple gastrointestinal pathogens from a single sample of feces. The Luminex xTAG Gastrointestinal Pathogen Panel (GPP) is a qualitative PCR that can simultaneously detect 11 different viral, parasitic or bacterial pathogens or toxins in stool specimens, including the following:

Bacteria and toxins
Campylobacter
Clostridum difficile Toxin A/B
Enterotoxigenic *E. coli* (ETEC) LT/ST
Shiga-like Toxin producing (STEC) E. Coli sfx1/sfx2
Salmonella
Shigella

Viruses
Norovirus GI/GII
Rotavirus A

Protozoa
Giardia
Cryptosporidium
Entamoeba histolytica

Systems sold in Canada and Europe also detect *Vibrio cholerae*, *Yersinia enterocolitica*, and adenovirus 40/41.

According to the FDA, "The manufacturer demonstrated the performance of the xTAG GPP by collecting samples from 1,407 patients with suspected infectious gastroenteritis and comparing the xTAG GPP results to individual tests that are known to separately and reliably detect the 11 viruses, bacteria, or parasites associated with the xTAG GPP. The manufacturer also ran the test on 203 samples from patients with previously confirmed infectious gastroenteritis, and 313 additional specimens from pediatric patients with suspected infectious gastroenteritis. Results were comparable to the individual tests. Due to the risk of false positives, all positive results from the xTAG GPP need to be confirmed by additional testing."

In Europe, the company reports the sensitivity of detection of individual pathogens is reported to range from 87.5% to 100%. Testing systems such as these represent significant advances, but will only be useful if they are readily available to the practicing clinician and are reasonably priced.

References

1. http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm335274.htm
2. http://www.luminexcorp.com/Products/Assays/ClinicalDiagnostics/xTAGGPP/index.htm *IDAlert* 1/15/2013 ■

Infectious Disease [ALERT]

Updates

By Carol A. Kemper, MD, FACP

High-dose flu vaccine in HIV+

McKittrick N, et al. Improved immunogenicity with high-dose seasonal influenza vaccine in HIV-infected persons. *Ann Intern Med* 2013;(158):19-26.

Data suggests that persons with HIV infection have lower rates of responsiveness to influenza vaccine compared with the rest of the population. In a preliminary study, protective antibodies were observed in 61% of HIV-infected persons who received H1N1 vaccine. To examine the immunogenicity of higher-dose influenza vaccine in patients with HIV-infection, these authors conducted a randomized double-blinded controlled clinical trial comparing high-dose (60 mcg/strain) vs standard dose (15 mcg/strain) trivalent influenza vaccine. Antibody titers were assessed at baseline and at 3-4 weeks post-vaccination (hemi-agglutination Ab titers ≥ 1:40 were considered sero-protective).

A total of 195 HIV+ persons were enrolled in the study;

190 completed the study; 97 received the higher dose of vaccine and 93 the standard dose. Most of the patients were receiving highly active antiretroviral therapy (88% in the high-dose group and 90% in the standard dose group), and most of them had HIV RNA levels < 400 copies/mL (89% vs 74% respectively). About 10% of participants had CD4 counts < 200 cells/mm3.

The higher dose vaccine did appear to be somewhat more immunogenic in this group of patients. For the H1N1 strain, 96% of the high dose group vs 87% of the standard dose group developed protective antibodies (p <.029); for Influenza H3N2, 96% of the high dose group vs the 92% of the standard dose group developed protective antibodies (p = NS); and for Influenza B, 91% of the high dose group vs 80% of the standard dose group developed protective antibodies (p < .03). The vaccines were similarly well-tolerated. There was a trend towards lower response rates in the few patients with CD4 counts < 200.

A surprising finding from this study was a higher than anticipated baseline rate of seropositivity to influenza, which probably contributed to the higher than anticipated vaccine response. About 50% of the patients in each group demonstrated baseline seroprotective antibody levels to H1N1, H3N2, and Influenza B (ranging from 44% to 52%) — in other words, about half of the patients were receiving a flu booster. ■

The Good News: HIV care is working (for those with access to care)

Moore RD, et al. Improvement in the health of HIV-infected persons in care: Reducing disparities. *Clin Infect Dis* 2012;55(9):1242-51.

Advances in HIV care in the United States, especially in disadvantaged people — and the ability to pay for that care, through such critical funding sources such as Ryan White — have made enormous differences in the success of treatment in persons with HIV infection. This article exemplifies the beneficial outcomes of good clinical HIV care and HIV therapeutics in a large urban disadvantaged population in Baltimore.

More than 6,366 patients have been cared for by the Johns Hopkins HIV/AIDS Service from 1995 to 2010, with a cumulative 27,941 person-years of follow-up. Since 1995, the percentage of patients receiving highly active antiretroviral therapy has increased from essentially zero (when such therapy was first introduced) to 87% in 2010. During this period of time, there was no apparent difference in the receipt of HAART based on gender, racial factors or risk group. Over that 15-year period, median CD4 counts have gradually increased and median HIV RNA levels have gradually decreased. By 2010, the median HIV RNA level was < 200 copies/mL — meaning that more than half of the patients were virologically suppressed. And, the median CD4 count had increased to 475 cells/mm3 – which means that half of the patients had essentially a normal number of CD4 cells. A dramatic decline in opportunistic infections was also observed during this period, and by 2010, only 2.4 OIs were documented per 100 patient-years. Mortality also fell to 2.1 per 100 patient-years.

Improvements in outcomes were observed in all patient groups with one exception: average CD4 counts were 76 cells/mm3 lower in patients with IDU compared with MSM; and their HIV RNA levels were on average 0.28 logs greater.

An important factor in the success of this HIV/AIDS program was the ability to retain patients in care — in 2010, 90% of patients remained in care throughout the year. This is despite findings that 73% of persons receiving care at the clinic fell below the federal poverty guideline. Improvements in HIV therapeutics — coupled with the ability to pay for that care — has been critical to the success of large, urban HIV clinics such as this. ■

The Sad News: Women at Risk for HIV (many without access to care)

Hodder SL, et al. HIV acquisition among women from selected areas of the United States: A cohort study. *Ann Intern Med* 2013; 158:10-18.

To explore the incidence of HIV infection and behavioral and demographic

risk factors for HIV in women at high risk for infection in the United States, these investigators enrolled 2099 high-risk women in a multi-state, longitudinal study for 6 to 12 months (study HPTN 064). They were recruited in 10 different high-risk urban areas throughout the United States. Most of the participants were black (86%) or Hispanic (12%). Criteria for inclusion in the study included 18-44 years of age; at least one episode of unprotected vaginal or anal sex with a man in the previous 6 months; residence in one of the designated high risk areas; and one or more risk factors for HIV (including incarceration, drug use, alcohol dependence, or a male partner with HIV, incarceration, drug use, or alcohol dependence).

A total of 8029 women were screened for the study; 3,233 (40%) were eligible and 2099 returned for enrollment. At entry to study, HIV was detected in 32 women, and 2 other women were found to have acute HIV-infection. Most of the participants (73%) reported both personal and partner risk factors for HIV; 34% reported 3 or more individual risk factors; and 87% reported partner risk factors.

To give an idea of how difficult it is to recruit and retain people into this kind of study, 466 women completed their 6-month visit. Despite the abundance of risk factors, only 4 women became HIV-positive during the study — which sounds like a relatively small number — but calculates out to be a 0.32% annual incidence of HIV infection. This figure is 640% greater than the current 2009 CDC estimate for the annual incidence of HIV infection in black women in the U.S. Remarkably, this study suggests that the risk for HIV-infection in the group of urban, largely black women living in the U.S. is comparable to adults living in sub-Saharan Africa!

Another sad revelation from this study was the high rate of mortality in study participants — 10 women died during the study period (annual mortality rate, 0.61%) — which is also significantly greater than age-adjusted mortality estimates for this age group. Causes of death included diabetic coma, HIV/AIDS, drug overdose, and homicide. The single greatest risk factor for death was drug use (excluding marijuana use). Twenty percent of the women reported they could not obtain health care — most often because they did not know where to find it, how to pay for it, or thought that care was not available. ■

Sex, Lies, and Technology

Http://www.salon.com/2103/01/15/safe_sex_theres_an_app_for_that/

The internet age has brought all kinds of conveniences and apps for your smart phone, from the popular app "GRINDR" (allowing you a speedy hook-up with the nearest sexually available individual) to the newest MedXSafe, which allows you to literally "bump phones" and share confidential STD and HIV info before you bump into bed. The phone app provides documentation from your doctor of your STD and HIV-disease-free status, just in case your new sexual partner demands certified proof. Apparently you get tested, you then ask your doctor to go to the website, and vouch for your negative lab tests. Of course, a negative test a month ago is no guarantee that an individual might not have since contracted something — or was the "window period" — and be potentially highly contagious.

Aside from the fact that physicians may object to logging on to this site and providing this information — and it's not clear how the site verifies the credibility of the physician — the website can only provide verification for negative tests — not positive ones, which seems a real limitation. Since the company states the information is secure, wouldn't it be helpful to provide positive test results as well? Since data suggests that up to 75% of sexually active HIV-seropositive MSM (defined as 2 or more partners in the previous 3 months) find it difficult to disclose their HIV seropositive status, wouldn't this be a great way to discreetly clue your potential partner into your status, and verify "HIV-compatibility", without really having to discuss it ? ■

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 health care providers has an indication for testing for active HBV infection prior to vaccination?

A. An individual whose mother was born in China, a country with a high prevalence of HBV infection.
B. An individual who performs orthopedic surgery.
C. An individual who performs vaginal deliveries.
D. All of above.

2. Which of the following is correct with regard to Borrelia myamotoi?

A. It is in the same taxonomic group as *Borrelia hermsii*, a cause of relapsing fever in North America.
B. It has never been identified outside North America.
C. It has never been identified in ticks in North America.
D. It is transmitted by body lice.

3. Which of the following is correct with regard to Epstein-Barr virus infection in college students?

A. Coitus is a greater risk factor than deep kissing.
B. The severity of disease correlates with the quantity of EBV DNA in whole blood, the number of CD8+ T cells, and granzyme B expression.
C. The severity of disease correlates with the quantity of EBV DNA in whole blood, the number of CD8+ T cells, but not granzyme B expression.
D. The severity of disease correlates with the quantity of EBV DNA in whole blood, granzyme B expression, but not the number of CD8+ T cells.

CME OBJECTIVES

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

- discuss the diagnosis of infectious diseases;
- explain current data regarding the use of new antibiotics for commonly diagnosed diseases and new uses for traditional drugs;
- discuss the latent 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]

Fidaxomicin "Chaser" regimen following vancomycin for patients with multiple *Clostridium difficile* recurrences

Diagnosis and management of prosthetic joint infection: IDSA clinical practice guidelines

Infection prevention during prolonged human space travel

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.*

FDA Approves Apixaban for Patients with Nonvalvular AF

In this issue: Apixaban approval; new dental clinical practice guideline; apixaban for VTE; aspirin resistance; tamoxifen treatment; and FDA actions.

Apixaban superior to warfarin in trial

The FDA has approved apixaban — the long-awaited third novel oral anticoagulant (NOAC) — for the prevention of stroke and systemic embolism in patients with nonvalvular atrial fibrillation (AF). The drug follows dabigatran (Pradaxa) and rivaroxaban (Xarelto) for this indication, which has been traditionally treated with warfarin. The safety and efficacy of apixaban was demonstrated in the 18,000 patient ARISTOTLE trial, which showed that in patients with nonvalvular AF, apixaban was superior to warfarin in preventing stroke and systemic embolism, caused less bleeding, and resulted in lower mortality than warfarin. The FDA will likely allow the manufacturers of apixaban to market the drug as "superior to warfarin." Apixaban is dosed twice a day, similar to dabigatran; rivaroxaban is dosed once a day. Apixaban and rivaroxaban are factor Xa inhibitors, while dabigatran is a direct thrombin inhibitor. No head-to-head studies have been done among the three NOACs, which are expected to compete aggressively for this lucrative market that is worth billions of dollars in sales. All three lack a reversal agent, which could potentially increase the risk of serious bleeding. Apixaban is marketed as Eliquis by Bristol-Myers Squibb and Pfizer. ■

New dental prophylaxis guideline

The American Academy of Orthopedic Surgeons (AAOS) and the American Dental Association (ADA) have jointly published a clinical practice guideline regarding dental prophylaxis in patients with orthopedic implants. The recommendations, which are based on very limited evidence, state that, "the practitioner might consider discontinuing the practice of routinely prescribing prophylactic antibiotics for patients with hip and knee prosthetic joint implants undergoing dental procedures." The guideline further states that they are unable to recommend for or against topical oral antibiotics in patients with implants, but they do recommend that patients with joint implants should "maintain appropriate oral hygiene," even though there is no evidence regarding this recommendation. This guideline does little to settle the debate between orthopedic surgeons, who often recommend lifetime dental prophylaxis, and infectious disease specialists who generally recommend against dental prophylaxis after 1 year. This rather weakly worded guideline is probably not the guidance most primary care physicians were hoping for, since they are generally responsible for prescribing prophylactic antibiotics and are responsible for possible adverse effects. The full guideline is available at www.aaos.org/research/guidelines/PUDP/dental_guideline.asp. ■

Length of treatment for VTE

How long should we treat patients with venous thromboembolism (VTE)? VTE includes deep-vein thrombosis and pulmonary embolism. Current

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guidelines recommend 3-6 months of anticoagulation for unprovoked VTE — usually low-molecular weight heparin followed by warfarin. A new study suggests that an additional year of the factor Xa inhibitor apixaban (recently approved for stroke prevention in nonvalvular atrial fibrillation, see page 1) may be beneficial for these patients. In an industry-sponsored study, patients with VTE who had completed 6-12 months of anticoagulation therapy were randomized to an additional 12 months of apixaban (2.5 or 5 mg twice a day) or placebo. Nearly 2500 patients were included in the intention-to-treat analysis. Recurrent VTE or death from VTE occurred in 73 of 829 patients randomized to placebo (8.8%) compared to 14 of 840 patients on 2.5 mg of apixaban (1.7%) and 14 of 813 patients on 5 mg of apixaban (1.7%; $P < 0.001$ for both comparisons). The rates of major bleeding were 0.5% in the placebo group and 0.2% and 0.1% in the apixaban 2.5 mg and 5 mg groups, respectively. The rate of death from any cause was 1.7% in the placebo group and 0.8% and 0.5% in the apixaban 2.5 mg and 5 mg groups, respectively. The authors conclude that extended anticoagulation with apixaban at either a treatment dose (5 mg bid) or thromboprophylactic doses (2.5 mg bid) reduced the risk of recurrent VTE without increasing the rate of major bleeding (*N Engl J Med* published online Dec. 8, 2012. doi: 10.1056/NEJMoa1207541). In this study, the majority of patients were younger than age 75 without other comorbities such as low body weight or renal impairment. It is also unknown if the results of this study are applicable to other approved anticoagulants such as rivaroxaban. ■

Aspirin resistance and enteric coating

Could "aspirin resistance" be due to enteric coating? The concept of aspirin resistance is very controversial with some experts suggesting that it does not exist. A new study suggests that enteric coating of aspirin may be partially responsible for "pseudoresistance." Researchers recruited 400 healthy volunteers who were then screened for their response to a single, oral dose of 325 mg immediate-release or enteric-coated aspirin. Variable absorption caused nearly half of those taking enteric-coated aspirin to have apparent resistance (49%), while this was not seen in any of the subjects taking immediate-release aspirin. On re-exposure, all of those with variable absorption responded to aspirin. The authors conclude that the study failed to identify a single case of true aspirin resistance, but pseudoresistance, reflecting delayed and reduced drug absorption, complicates enteric-coated but not immediate-release aspirin (*Circulation* published online Dec. 4, 2012. doi: 10.1161/CIRCULATIONAHA.112.117283). This study seems to contradict the concept that up to 40% of the population is "aspirin resistant." There is a suggestion that the concept of aspirin resistance has been touted by the manufacturers of expensive brand-name aspirin substitutes. This study may question the wisdom of the routine use of enteric-coated aspirin, especially given that enteric coating has very little benefit with regard to gastrointestinal protection. ■

Is 10 years of tamoxifen better?

Ten years of tamoxifen may be better than the standard 5 years for women with estrogen receptor (ER)-positive breast cancer, according to a new study from the United Kingdom. Researchers randomized about 6800 ER-positive women with early breast cancer who had completed 5 years of adjuvant tamoxifen to another 5 years of treatment or stopping therapy. There were 617 recurrences in the 3428 women who took tamoxifen for 10 years vs 711 in 3418 women who stopped at 5 years ($P = 0.002$). There was also a lower death rate (331 vs 397, $P = 0.01$) and reduced overall mortality (639 vs 722, $P = 0.01$) in the 10-year group. There were higher rates of endometrial cancer (relative risk [RR] 1.74, 95% confidence interval [CI], 1.30-2.34) and pulmonary embolism (RR 1.87; CI, 1.13-3.07) in the 10-year group, but no higher rate of stroke and a lower risk of ischemic heart disease (RR 0.76; CI, 0.60-0.95). The authors suggest that 10 years of tamoxifen in ER-positive patients can approximately halve breast cancer mortality during the second decade after diagnosis (*Lancet* published online Dec. 5, 2012. doi.org/10.1016S0140-6736(12) 61963-1). ■

FDA actions

The FDA has approved pasireotide diaspartate injection for the treatment of Cushing's disease in patients who are not candidates for surgery or for whom surgery has not worked. The drug is considered an orphan drug. The safety and efficacy were evaluated in a trial of 162 patients with Cushing's disease who were randomized to one of two doses of the drug. About 20% of participants had normal urine cortisol levels within 6 months. Side effects included increased blood sugar levels and liver injury. The drug is administered subcutaneously twice a day. It is marketed by Novartis as Signifor. In February 2012, the FDA approved mifepristone (Korlym) for the treatment of Cushing's syndrome. ■