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INSIDE

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Olsetamivir for Children 1-3 Years of Age

ABSTRACT & COMMENTARY

By Hal B. Jenson, MD, FAAP

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

Synopsis: *Oseltamivir treatment initiated within 24 hours of onset of influenza symptoms among children 1-3 years of age provides significant benefits for resolution of illness, and reduces the risk for development of acute otitis media if started within 12 hours.*

Source: Heinonen S, et al. Early oseltamivir treatment of influenza in children 1-3 years of age: A randomized controlled trial. *Clin Infect Dis.* 2010;51:887-894.

A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL OF THE EFFICACY OF oral oseltamivir twice daily started within 24 hours of onset of influenza symptoms (fever, plus cough, rhinitis, or sore throat) was conducted in children 1-3 years of age at a single primary care study site in Finland during the 2007-2008 and 2008-2009 influenza seasons. Of 208 children who were enrolled, (oseltamivir, 203; placebo, 205), 98 had laboratory-confirmed influenza (influenza A, 79; influenza B, 19). The mean age of these 98 children was 2.4 years, and 13 (13.3%) had received influenza vaccine for the season.

When started within 24 hours of onset of symptoms, oseltamivir shortened the median time to resolution of symptoms by 3.5 days (3.0 vs. 6.5 days, $p = 0.002$) in vaccinated children and by 4.0 days in unvaccinated children (3.4 vs. 7.3 days, $p = 0.006$), and reduced parental work absenteeism by 3.0 days. When started within 12 hours of onset of symptoms of influenza A, oseltamivir decreased the incidence of acute otitis media by 85% (95% CI, 25-97%), with no significant difference if started 12-24 hours after onset of symptoms. There were too few cases of influenza B to demonstrate efficacy.

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■ **COMMENTARY**

Influenza is an important childhood disease, with rates of influenza-associated hospitalization among children < 2 years of age comparable to other high-risk groups, such as adults ≥ 65 years of age, pregnant women, and persons with chronic pulmonary or cardiac disease. The burden of influenza is significant, with estimates that medical visits among children < 5 years of age with influenza account for 10%-19% of office visits and 6%-29% of emergency department visits.

Oseltamivir, formulated as capsules or oral suspension (Tamiflu), is FDA-approved for prophylaxis and empiric treatment of influenza in patients ≥ 12 months of age. The FDA issued an Emergency Use Authorization for oseltamivir prophylaxis in patients < 12 months of age as part of the public health emergency declaration in 2009 for H1N1 influenza, which expired June 23, 2010.

This study demonstrates that oseltamivir treatment initiated within 24 hours of onset of influenza symptoms provides significant benefits for resolution of illness, and reduces the risk for development of acute otitis media if started within 12 hours. There is also a significant corresponding reduction of parental-work absenteeism. This is an important economic and social consideration for clinicians in these times with both parents in many families working outside the home, as well as with many single-parent families.

The diagnosis of influenza in children requires much interpretation of symptoms by the clinician. For example, the criteria used in this study for influenza symptoms included rhinitis and cough; objective measures for these symptoms in young children are not clearly established and remain subjectively applied. The study criteria also included "sore throat." Since only the patient can determine if the throat is "sore," it seems wildly optimistic to expect a child 1-3 years of age to convey this with precision and accuracy, let alone the clinician's dilemma of understanding what a 3-year-old child might mean if they do answer yes to having a "sore throat." In children, other viruses, such as respiratory syncytial virus and parainfluenza viruses, lead to the same symptoms, as evidenced in this study, with one-quarter (24.7%) of enrolled patients meeting symptom criteria having laboratory-confirmed influenza A or B. Nevertheless, even with these inherent limitations, this study demonstrated utility in empiric oseltamivir treatment. Development and availability of better rapid diagnostic tests for influenza viruses and other respiratory tract pathogens are needed to facilitate prompt diagnosis and appropriate management. ■

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Trading Kidney Disease for Protection from Trypanosomiasis

ABSTRACT & COMMENTARY

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Dr. Winslow is on the speaker's bureau for GSK and Cubist Pharmaceuticals, and is a consultant for Siemens Diagnostics.

Synopsis: *Two apolipoprotein L1 (ApoL1) variants were found to be associated with focal segmental glomerulosclerosis (FSGS) and hypertension-attributed end-stage kidney disease (H-ESKD) in African-American patients. These two ApoL1 variants (G1 and G2) were common in controls from Africa but were not present in European chromosomes. In-vitro assays showed that only kidney disease-associated ApoL1 lysed* Trypanosoma brucei *rhodesiense.*

Source: Genovese G, et al. Association of trypanolytic ApoL1 variants with kidney disease in African-Americans. *Science*. 2010;329:841-845.

Initial association analysis was performed on 205 African-americans with biopsy-proven FSGS and 180 African-American controls. A two-locus allele, G1, in the last exon of ApoL1, was found to have a frequency of 52% in FSGS cases and 18% in the controls. By using logistic-regression analysis to control for G1, a six base-pair deletion near G1 (termed G2) was also found to be strongly associated with FSGS. Next, a larger cohort of 1,030 African-American cases with H-ESKD and 1,025 African-American controls from the Southeastern United States were examined. Again, G1 and G2 were found to be strongly associated with kidney disease. Using other available sequence data, G1 was found in 40% of Yoruba tribesmen (Nigeria in West Africa) and in a smaller number G2 was found. These alleles were not seen in individuals of European, Japanese, or Chinese background. In-vitro trypanolytic activity of plasma from 75 individuals with different combinations of G1 and G2 genotypes was determined. All samples efficiently lysed *T. brucei brucei*, but none lysed *T. brucei gambiense*. Serum-resistant *T. brucei rhodesiense* was more efficiently lysed by G2 than G1 plasma, although both homozygous, heterozygous variants and G1/G2 double-heterozygous plasma resulted in lysis of trypanosomes. These results were confirmed in trypanolytic experiments using recombinant ApoL1 proteins.

■ **COMMENTARY**

Innate immunity to *T. brucei brucei* is due to the trypanolytic activity of a human-specific apolipoprotein bound to high-density lipoproteins, termed ApoL1. This protein contains an ionic pore-forming domain consisting of nine alpha helixes and a pH-sensitive membrane-addressing domain consisting of two alpha helixes. ApoL1 is taken up by the trypanosome, and the resultant pore formation and loss of osmotic stability results in lysis. *T. brucei rhodesiense* and *T. brucei gambiense* have acquired resistance to ApoL1. Resistance to lysis in normal human serum in *T. brucei rhodesiense* is conferred by a single protein, serum-resistance-associated protein (SRA), which binds specifically to ApoL1. The mechanism of serum resistance of *T. brucei gambiense* is not known. Another hemoflagellate that infects domestic animals, *T. evansi*, is generally not pathogenic for humans, although a case of human infection due to *T. evansi* was recently reported in India, and subsequent investigation revealed the patient lacked ApoL1.[1] Another recent paper shows that ApoL1 may also be implicated in innate anti-Leishmania activity.[2]

I thought this was a fascinating paper. The data show that sequence variation in ApoL1 contributes to the increased prevalence of renal disease in African-Americans (most came to the United States originally as slaves captured or sold from West Africa). While the mechanism of the association between the G1 and G2 variants and renal disease has yet to be defined, the data suggest that ApoL1 performs a critical role in the kidney and that it is impaired in the setting of ApoL1 variants (or that these variants may directly cause kidney toxicity). The data also show that both the G1 and G2 variants effectively lyse a *T. brucei rhodesiense* subspecies that is normally resistant to serum ApoL1 lytic activity. These kidney disease-associated variants are located on haplotypes that the authors state show statistical evidence of natural selection and these ApoL1 risk alleles occur in more than 30% of African-Americans. Elucidating the molecular mechanisms by which these alleles contribute to renal injury will make for some very interesting science of great potential relevance to treating or preventing kidney disease in patients of African origin. ■

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Pertussis Prevention

SPECIAL FEATURE

By Stan Deresinski, MD, FACP

The introduction of accellular pertussis vaccines represented an important advance in public health, but developing a vaccine is not synonymous with protecting a population. The latter involves convincing health-care providers (HCPs) and the targeted populations of its safety and efficacy and making the vaccine readily available. The uptake of the pertussis vaccine is somewhat complicated by the fact that it is only available in combination with diphtheria and tetanus toxoids — DTaP is licensed for infants and young children and Tdap (**t**etanus, **d**iphtheria, **a**cellular **p**ertussis) for those 10-64 years of age. The Advisory Committee on Immunization Practices (ACIP) in 2005 recommended that Tdap replace the standard Td for the latter group.

The CDC has analyzed data from the National Health Interview Survey (NHIS), and found that the self-reported tetanus vaccination coverage was 60.4%

in 1999 and 61.6% in 2008 among adults ages 18-64 years.1 Of those reporting vaccination during 2005-2008, 52% reported receiving Tdap, but total Tdap coverage in 2008 was only 5.9%. Even worse, only 15.9% of HCP and 5.0% of individuals with infant contact reported having received Tdap.

The effects of these low reported rates of uptake of Tdap are reflected in the current situation in California. As of August 24, a total of 3,311 confirmed, probable, and suspected cases had been reported during 2010, corresponding to a rate of 8.5 cases/100,000 population.[2] This was a seven-fold increase from the number of reported cases during the same time period in 2009, when just 454 cases were reported, and is the largest number of cases in California since 1958. Case rates were highest in infants < 6 months of age (158 cases/100,000), and in adolescents aged 7-9 years (26 cases/100,000), and 10-18 years (20 cases/100,000). Twelve percent of cases have required hospitalization. Sixty percent of hospitalized patients were infants < 3 months of age, with three-fourths of these being < 6 months of age. Eight deaths have been reported, seven of which were in infants < 2 months of age at time of disease onset; none had received any doses of pertussis-containing vaccine. The eighth fatality was a 28-week preemie who was 2 months of age, who had received the first dose of DTaP 11 days prior to disease onset.

Pertussis (whooping cough) is spread by inhalation of respiratory droplets or aerosols and is highly contagious — each patient is believed to infect, on average, more than a dozen individuals, and infants are highly vulnerable. Infants are protected from many infections during their first months of life as the result of the transfer of maternal antibodies during gestation. Unfortunately, unless recently immunized, most pregnant women have waning of immunity to pertussis and are unable to provide sufficient protective antibody to their fetus. As a consequence, the California Department of Public Health (CDPH) recommends that all women of childbearing years be vaccinated with Tdap vaccine. Pregnancy is not a contraindication to vaccination,[3] although vaccination is commonly deferred until the 2nd or 3rd trimester, or immediately postpartum. In addition, all other close contacts of infants, including family members, caregivers, and HCPs should also be vaccinated at least two weeks before contact. CDPH recommends that all health care personnel, particularly those who have direct contact with infants and pregnant women, be immunized with Tdap to protect their patients and themselves. This strategy provides a "cocoon" of safety for the infant.

The first dose of DTaP, the vaccine version for infants and young children, has been typically given at 2 months of age but may be given as early as 6 weeks to provide protection earlier in life. CDPH recommends that vaccination with Tdap include critical groups for whom Tdap is not licensed, including children 7-9 years of age and individuals ≥ 65 years of age. Children 7-9 years of age who had not received all of their routine childhood DTaP vaccine doses are recommended to receive Tdap. Those ≥ 65 years of age are important because of the potential role of grandparents in transmission to infants. Pertussis in adults usually does not have the severe whooping cough characteristically seen in infants and young children and, as a consequence, frequently goes undiagnosed. Nasopharyngeal cultures are the gold standard for diagnosis, but are quite insensitive; the optimal single test is detection of *Bordetella pertussis* nucleic acid by PCR. Serological testing is generally not recommended.

Because of its lack of licensure in those ≥ 65 years of age, questions have arisen regarding Medicare coverage. Tdap vaccine is covered by Medicare Part D, and may be obtained by Part D beneficiaries from a network pharmacy without out-of-pocket costs to the beneficiary. Tdap may also be provided in a network provider's office; however, this would require the beneficiary to pay for the vaccine costs up front and then be reimbursed by his or her Medicare Part D plan. It is recommended that beneficiaries should contact their Medicare Part D plan in advance for detailed instructions on reimbursement for Tdap vaccination.

The resurgence of pertussis is a reminder that we have not conquered all childhood diseases in the United States. Reasons for the continuing and worsening pertussis problem include the lack of lasting immunity after vaccination (as well as after natural infection), the lack of passively transferred protective antibody in most infants, and the role of adults as reservoirs for transmission. As HCPs, we all have an obligation to actively promote pertussis vaccination, including for ourselves, in order to protect our patients and families. ■

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Antibiotic Use During Pregnancy and Risk of Birth Defects

ABSTRACT & COMMENTARY

By Jeffrey T. Jensen, MD

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Dr. Jensen receives research support from, is a consultant to, and serves on the speaker's bureau of Bayer Healthcare/Bayer Schering; he also receives research support from Wyeth and Warner-Chilcott, and is a consultant to Schering Plough.

This article originally appeared in the July 2010 issue of OB/GYN Clinical Alert. *It was peer reviewed by Catherine LeClair, MD. Dr. LeClair is Associate Professor, Oregon Health & Science University; she reports no financial relationships relevant to this field of study.*

Synopsis: *First trimester exposure to nitrofurantoin and sulfonamides was associated with an increase in the risk of several birth defects including cleft lip and palate in the National Birth Defects Prevention Study.*

Source: Crider KS, et al. Antibacterial medication use during pregnancy and risk of birth defects: National Birth Defects Prevention Study. *Arch Pediatr Adolesc Med* 2009;163: 978-985.

The purpose of this study was to estimate the association between antibacterial medications and selected birth defects. The authors conducted a population-based, multisite, case-control study of women who had pregnancies affected by one of more than 30 eligible major birth defects identified via birth-defect surveillance programs. The study population included 13,155 cases of women with affected pregnancies and 4,941 control women with unaffected pregnancies randomly selected from the same geographical regions (10 states). The main exposure reported was maternal use of antibacterials (one month before pregnancy through the end of the first trimester), and odds ratios (ORs) measuring the association between antibacterial use and selected birth defects were constructed and adjusted for potential confounders. The reported use of antibacterials increased during pregnancy, peaking during the third month.

Sulfonamides were associated with anencephaly (adjusted OR [AOR] = 3.4; 95% confidence interval [CI], 1.3-8.8), hypoplastic left heart syndrome (AOR = 3.2; 95% CI, 1.3-7.6), coarctation of the aorta (AOR = 2.7; 95% CI, 1.3-5.6), choanal atresia (AOR = 8.0; 95% CI, 2.7-23.5), transverse limb deficiency (AOR = 2.5; 95% CI, 1.0-5.9), and diaphragmatic hernia (AOR = 2.4; 95% CI, 1.1-5.4).

Nitrofurantoins were associated with anophthalmia or microphthalmos (AOR = 3.7; 95% CI, 1.1-12.2), hypoplastic left heart syndrome (AOR = 4.2; 95% CI, 1.9-9.1), atrial septal defects (AOR = 1.9; 95% CI, 1.1-3.4), and cleft lip with cleft palate (AOR = 2.1; 95% CI, 1.2-3.9).

Other antibacterial agents were not associated with a significant increase in the AOR of these birth defects. The authors concluded that sulfonamides and nitrofurantoins were associated with several birth defects, indicating a need for additional scrutiny. In contrast, penicillins, erythromycins, and cephalosporins appeared to be safer alternatives.

■ COMMENTARY

The National Birth Defects Prevention Study (NBPS) is conducted by investigators at the Centers for Disease Control and Prevention. This large representative, multistate database is about as good as we get in the current United States' health-care system to assess exposure and rare outcomes in a large population-based, classic case-control study. While case-control studies cannot demonstrate a causal relationship, they can suggest important relationships worthy of additional consideration. For the assessment of rare outcomes, where prospective, randomized studies are impractical, they provide the best evidence for clinical guidance.

Case-control studies are always subject to confounding. Common events, such as urinary tract infections (UTIs), will lead to multiple exposures, and common drugs will be widely used. Recall bias further complicates studies of exposure, as those women who experience an abnormal pregnancy may have a greater tendency to report exposure or to recall the drug they were treated with.

More than 2% of women in this study were treated for a UTI in the first trimester. The authors designed their assessment to critical exposure during the period of early fetal development. Still, many of the abnormalities are restricted to an even more limited time of exposure, with most structural anomalies occurring before six weeks of gestation.[1] The majority of subjects in the NBPS were treated between 8-13 weeks, well after the expected developmental critical windows for the listed anomalies.

However, the most commonly used antibiotics —

penicillins, erythromycins, and cephalosporins (all FDA pregnancy category B) — were not associated with an increased risk of anomalies in this study, while both nitrofurantoin and sulfonamides were associated with significant increased AOR of risk for a variety of anomalies. Sulfonamides (FDA pregnancy category C or D) have been shown to be teratogenic in animal studies, although it is unclear whether sulfonamides without trimethoprim pose a significant risk.[2] The two drugs act synergistically to block two steps in the biosynthesis of reduced folates, and other case-control studies have demonstrated an increased risk of anomalies with first trimester exposure.[3] These drugs can also affect bilirubin metabolism and should not be used in the third trimester and while breast feeding. The observed increase in risk with nitrofurantoin (Category B) is more surprising. The drug primarily concentrates in the urinary tract, and has not previously been associated with fetal harm. It is well tolerated, easy to take, and highly effective against most pathogens.

Taken together, the results from this study are far from conclusive. Since there are alternatives to use of nitrofurantoins and sulfa/trimethoprim in the first trimester, it is wise to do so even if the evidence is limited. Also, avoid sulfonamides in the third trimester to avoid the known association with hyperbilirubinemia.

A more important consideration is the reproductive age non-pregnant patient who presents or calls with UTI symptoms. Is it safe to use nitrofurantoin or sulfa drugs in these women? In contrast to the patient at eight weeks, these are exactly the individuals in whom an early fetal exposure is possible. Consider carefully the drug resistance patterns in your community and the contraceptive status of your patient when considering therapy. If she is at high risk for pregnancy, it is best to avoid these drugs. ■

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Updates on Recommendations for Use of Human Papillomavirus Vaccines

ABSTRACT & COMMENTARY

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

This article originally appeared in the August 2010 issue of Travel Medicine Advisor. *It was edited and peer reviewed by Frank J. Bia, MD, MPH. Dr. Bia is Professor (Emeritus) of Internal Medicine (Infectious Disease and Clinical Microbiology), Yale University School of Medicine.*

Synopsis: *A new bivalent HPV vaccine is now licensed for use in females aged 10-25 years, and the quadrivalent HPV vaccine is now licensed for use in males aged 9-26 years in the United States.*

Sources: CDC. FDA licensure of bivalent human papillomavirus vaccine (HPV2, Cervarix) for use in females and updated HPV vaccination recommendations from the Advisory Committee on Immunization Practices (ACIP). *MMWR.* 2010;59:626-629; CDC. FDA licensure of quadrivalent human papillomavirus vaccine (HPV4, Gardasil) for use in males and guidance from the Advisory Committee on Immunization Practices (ACIP). *MMWR.* 2010;59: 630-632.

In October 2009, the FDA licensed the bivalent human papillomavirus vaccine (HPV2; Cervarix, GlaxoSmithKline) for use in females aged 10 through 25 years. This vaccine joins the quadrivalent HPV4 vaccine (Gardasil, Merck & Co) that was licensed in 2006 for use in females aged 9 through 26 years. Both HPV2 and HPV4 are composed of virus-like particles (VLPs) prepared from recombinant L1 capsid protein of HPV. Neither vaccine is a live vaccine. HPV2 and HPV4 include protection against HPV 16 and HPV 18, the two oncogenic HPV types that together account for 70% of cervical cancers. In addition, HPV4 protection includes HPV 6 and HPV 11, the two nononcogenic types that account for 90% of genital warts and most cases of recurrent respiratory papillomatosis.

The approval of HPV2 came after review of efficacy data in two randomized, double-blind, controlled clinical trials in females aged 15 through 25 years. One study was a phase IIb study, and the other was a phase III trial.[1] The phase III trial included 18,644 females who were followed for a mean of 34.9 months. According to the protocol analysis, the efficacy against HPV 16 or 18 related cervical intraepithelial neoplasia grade 2 or 3 or adenocarcinoma in situ (CIN2+) was 92%.[2] In both studies, greater than 99% of participants developed an HPV 16 and 18 antibody response 1 month after completing the 3-dose series.

ACIP recommends routine vaccination of females aged 11 or 12 years with 3 doses of either HPV2 or HPV4, but vaccination may be initiated as early as age 9, ideally before potential exposure to HPV through sexual contact. The antibody response after co-administration with Tdap (tetanus toxoid, diphtheria, and acellular pertussis) and meningococcal conjugate vaccine (MCV4) was noninferior for all vaccine antigens. Therefore, these vaccines can be administered at the same time, such as during a routine adolescent visit.

The three-dose schedules for HPV2 and HPV4 vaccines are the same, namely 0, 1-2 months, and 6 months. The minimum interval between the first and second dose is 4 weeks. If the series is interrupted for any reason, the series does not need to be restarted. For example, if the series is interrupted after the first dose, the second dose should be administered as soon as possible, and the second and third doses should be separated by an interval of at least 12 weeks with a minimum interval of 24 weeks between first and third doses. Vaccine doses received after a shorter-than-recommended dosing interval should be repeated.

The FDA also licensed the HPV4 vaccine for use in males aged 9 through 26 years for prevention of genital warts (condyloma acuminata) caused by HPV types 6 and 11. A phase III efficacy study enrolled 4,065 males aged 16 through 26 years from North and South America, Europe, Australia, and Asia with a median duration of follow-up of 2.3 years. The efficacy for prevention of genital warts related to HPV types 6, 11, 16, or 18 in the per protocol population (i.e., patients who received all 3 vaccine doses, were seronegative at day 1, and DNA negative day 1 through 7 to the respective HPV type) was 89.4%. The efficacy in the intent to treat population (males who received at least one vaccine dose regardless of baseline DNA or serology) was 67.2%.[3] Seroconversion rates were high for all four HPV types (HPV 6, 11, 16, 18) after vaccination with HPV4, but antibody titers were significantly higher in males aged 9 through 15 years compared with males aged 16 through 26 years.

■ COMMENTARY

The approval of HPV4 vaccination for use in males is important in the ongoing effort to reduce the overall health burden of conditions associated with HPV. At this point, the ACIP is not recommending routine use of HPV4 in males, likely in part because mathematical modeling suggests that male HPV vaccination in addition to female-only vaccination is cost-effective only when vaccine coverage of females is less than 80%.[4] However, data do show HPV4 has a high efficacy for prevention of intraepithelial neoplasias in men who have sex with men (MSM).[5] Therefore, this may be an appropriate group in whom to first focus the use of HPV4 vaccine in males.

The vaccine schedules, administration, and potential adverse effects of HPV2 and HPV4 in males and females are similar, which is helpful for health care providers with the increasing complexity of childhood and adolescent vaccine schedules. The post-marketing addition of a warning of possible syncope associated with HPV4 vaccination led to the recommendation of a 15-minute period of observation after vaccine administration. Local injection site reactions were noted in 83.9% of females and 61.5% of males during HPV4 studies, but more than 94% of both groups judged their injection-site adverse reactions to be only mild to moderate in intensity.[3]

The HPV2 and HPV4 vaccines can be co-administered with any live or inactivated vaccine since neither is a live vaccine and both can be administered to immunocompromised patients. They are both category B for use in pregnancy since animal studies showed no evidence of impaired fertility or harm to the fetus. There are very limited data on use of HPV vaccine in lactating women. Since the vaccine consists of viral capsid proteins it is unlikely to have an adverse effect on the infant and therefore is not contraindicated in breastfeeding women.[6] HPV4 is produced in baker's yeast (*Saccharomyces cerevisiae*) and is therefore contraindicated in persons with an immediate hypersensitivity to yeast. The pre-filled syringes of HPV2 have a latex rubber stopper and therefore should not be used in patients with an anaphylactic latex allergy. These patients can receive HPV2 from single-dose vials, which do not contain any latex. ■

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Tungiasis – Painful Feet in a Tropical Traveler

ABSTRACT & COMMENTARY

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

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Dr. Barry is a consultant for the Ford Foundation, and her program receives funding from the Johnson & Johnson Corporate Foundation. Dr. Blackburn reports no financial relationships relevant to this field of study.

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Synopsis: *Tungiasis is an ectoparasite caused by the impregnated female sand flea Tunga penetrans. This is a case report of a traveler who presented with painful foot lesions after spending four weeks in the Pantanal region of Brazil.*

Source: Hakeem MJML, Morris AK, Bhattacharyya DN, et al. Tungiasis — A cause of painful feet in a tropical traveler. *Travel Medicine and Infectious Disease.* 2010;8:29-32.

A 39-YEAR-OLD MAN HAD TRAVELED FOR FOUR WEEKS TO THE Pantanal region of Brazil, a popular ecotourism area, where he had walked barefoot on several occasions. Ten days before returning to the UK, he noted painful lesions on his feet that were white/pale yellow with a central black punctum. He was afebrile and had no associated lymphadenopathy. Microscopy of excised samples confirmed *Tunga penetrans* infestation.

■ COMMENTARY

Tungiasis is a parasitic skin infestation caused by the female sand flea T. penetrans, or Chigoe flea, which burrows into the epidermis of the host. The flea is endemic in Central and South America as well as the West Indies and sub-Saharan Africa. Its main habitat is warm dry soil and sandy beaches, and the organism is more prevalent during the dry season. To reproduce, the flea requires a warm-blooded host. Domestic animals, rodents, and other wild animals may act as reservoir hosts, as can humans. Once impregnated, the female flea feeds on host blood and releases eggs after a one- to three-week period. Death of the flea follows, and the eggs hatch on the ground, become larvae, and pass through their life cycle.

Severe infestations of more than 100 sand fleas have been described, and secondary superinfection can occur. Surgical extraction of the fleas under sterile conditions is the most appropriate treatment, although oral ivermectin has been reported to be effective.[1] A subsequent randomized study has not confirmed the usefulness of ivermectin therapy for this condition.[2]

A complaint of painful feet with lesions occurring after a tropical trip has a defined differential diagnosis. Cutaneous larval migrans caused by dog and cat hookworm presents as very pruritic lesions, usually on the feet, and they often have a serpentine thread-like subcutaneous lesion that can move slowly through the skin. Botfly or Tumbu fly lesions present a boil-like lesion with a central opening where the larvae head can be seen and even coaxed out with bacon. Other painful foot considerations include verruca vulgaris (plantar warts), various mycoses, pyogenic infections, infected insect bites, dracunculiasis, and melanoma. In short, the best treatment of tungiasis is prevention by wearing shoes and socks as well as by using DEET repellent. The flea is a poor jumper and tends to penetrate the periungual area of the toes, heels, and soles of feet. Thus, flip-flops are not adequate for beach protection, and short socks and shoes should be considered for endemic areas. ■

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1. Veraldi S, Valsecchi M. Imported tungiasis: A report of 19 cases and review of the literature. *Int J Dermatol* 2007;46:1061-6.
2. Henkelbach J, Frank S, Feildmeier R, et al. Therapy of Tungiasis: A double-blinded randomized controlled trial with oral ivermectin. *Mem Inst Oswaldo Cruz* 2004;99:873-6

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. ■

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CME Questions

10. Which of the following is correct?

a. Tdap administration is contraindicated during pregnancy.

b. Tdap administration is contraindicated if the recipient is breast-feeding.

c. Tdap vaccination is indicated for infant care givers, including, e.g., elderly grandparents.

d. Tdap and Td are fully interchangeable vaccines.

11. Which of the following is correct regarding oseltamivir in children?

a. It is not FDA approved for administration to two-year-olds.

b. Its administration within 24 hours of symptom onset reduces the duration of symptoms by an average of 3.5 days.

c. Its administration did not prevent otitis media, even if initiated within 12 hours of symptom onset.

d. It is difficult to use in small children because it is only available in tablet form.

12. Which of the following was found to be associated with birth defects when administered during the first trimester of pregnancy?

a. Only sulfonamides

b. Only nitrofurantoin

c. Sulfonamides and nitrofurantoin

d. Sulfonamides and cephalexin

Answers: 10. (c); 11. (b); 12. (c)

In Future Issues:

Hepatitis D in Injection-drug Users

UPDATES

By Carol Kemper, MD, FACP

H1N1 in HIV Infection

Source: Perez CM, et al. Pandemic influenza A (H1N1) in HIV-infected patients. *AIDS*. 2010; 24: Epub ahead of publication.

Although there is little data to support this, I routinely counsel my HIV-infected patients to get seasonal and H1N1 vaccine, explaining that while they are probably at no greater risk for "catching the flu," they may be at greater risk for more severe symptoms and complications than someone without HIV.

During the first epidemic wave of H1N1 in Santiago, Chile between May and August 2009, the incidence and severity of influenza infection in the HIV clinic population was examined. During those months, a total of 1,720 HIV-infected patients sought clinical care in Santiago at six different clinical sites, 30 (1.74%) of whom were diagnosed with H1N1 influenza. The diagnosis was made on clinical grounds in 25 patients, and confirmed by PCR in five. The majority of influenza cases at that time were due to circulating H1N1.

Of the 30 patients, five had recognized risk factors for more severe influenza, including one pregnant patient, two with diabetes, one with hypertension, and one who was obese. Twenty-eight of the patients were receiving HAART therapy, and 23 patients (76.6%) had effective virologic suppression on antiretroviral therapy. The mean CD4 count was 423 cells/mm3 (range, 95 – 771 cells/mm3); two patients had CD4 counts < 200 cells/mm^3. Only 37% had received a seasonal flu vaccine.

All patients received antiviral therapy with oseltamivir (the pregnant patient received zanamivir). Symptoms on presentation were fairly typical, with more than 80% of patients presenting with fever, cough, and myalgias. Nearly one-fourth had gastrointestinal symptoms with vomiting and/or diarrhea. The mean duration of symptoms was 5.6 days. Four patients had abnormal chest radiographs consistent with either viral or bacterial pneumonia, two of whom required hospitalization. None of the patients required mechanical ventilation, and none died. In total, three patients (10%) required hospitalization; their average CD4 count was 506 cells/mm3.

This report suggests that the incidence of infection in HIV+ persons (1.74%) during a local outbreak of H1N1 is similar to that for non-HIV-infected persons. The risk for someone with HIV acquiring H1N1 is, therefore, probably not significantly greater than that of an otherwise healthy person without HIV. Compared with non-HIV-infected persons, the authors assert that the presentation and outcome for HIV-infected patients appears similar. However, in this report, which examines a small group of HIV-infected patients with influenza, the risk of hospitalization (10%) does appear greater than that of the general public. The risk of pneumonia and hospitalization in HIV-infected persons with H1N1 did not appear to be associated with the degree of immune deficiency, as reflected by the CD4 count. I will continue to counsel my HIV+ patients to get the flu shot.

Seizures in Children with H1N1

Source: Rellosa N, et al. Neurologic manifestations of pediatric novel H1N1 influenza infection. *The Pediatric Infection Disease Journal*. 2011;30: epub (ahead of print).

Neurologic manifestations of influenza virus infection are well recognized, ranging from seizures, encephalopathy and encephalitis, transverse myelitis, and acute disseminated encephalomyelitis (ADEM), to the rare but potentially devastating acute necrotizing encephalopathy (ANE). In fact, I just saw a 40-year-old computer engineer with persisting neurologic complaints following a recent episode of viral encephalomyelitis, believed to be secondary to influenza A infection. He was suffering from persistent gait disorder and tremors so severe, suggestive of residual basal ganglia impairment, he had trouble functioning at his job at the computer.

Neurologic involvement with H1N1 in children was first described in *MMWR* in May 2009 (*MMWR*. 2009;58:773-778), with a description of four children who developed mild encephalitis and seizures, all of whom fully recovered. CSF pleocytosis was absent in those cases. Subsequently, a number of other pediatric cases with neurologic involvement from H1N1 have been described in the literature, including one child who died from ANE, none with reported CSF pleocytosis.

These authors describe three children with severe neurologic manifestations and seizures from H1N1 influenza infection, two of whom developed mild lymphocytic pleocytosis. The children ranged in ages from 23 months to 9 years, and all were previously healthy (one had sickle cell trait). None of the children had received influenza vaccine, and all three had confirmed H1N1 infection by PCR of respiratory specimens. One child developed acute viral symptoms and, 4-5 days later, developed progressive confusion, loss of consciousness, and facial grimacing and twitching, with a diagnosis of encephalitis. EEG demonstrated partial complex status epilepticus, and MRI scanning was consistent with ADEM. He required critical care and phenobarbital coma for two weeks in the ICU but slowly recovered and was transferred to a rehab facility. He was left with a residual speech abnormality.

A second child developed a febrile illness nine days earlier and was treated for an ear infection. He then developed rapid onset of fever and frequent grand mal seizures, with ankle clonus on exam. He was hospitalized but quickly responded to antiviral and antiepileptic therapy and was released from the hospital fully recovered (before an MRI was performed). A third child was diagnosed with influenza H1N1 at a local urgent care center but received only a single dose of oseltamivir. Five days later he developed progressive lethargy with increasing seizure activity. MRI was consistent with bilateral increased signal intensity in the basal ganglia and thalamus. He quickly improved, with resolution of neurologic symptoms within six days on antiepileptic therapy.

The CSF results in two of the children demonstrated mild-to-moderate pleocytosis (12 to 32 cells/mm3), with a predominance of lymphocytes (85%-90%) and mildly increased protein levels; the 3rd had normal-appearing CSF, with only four WBC/mm3. CSF PCR for influenza A was negative in two of two patients tested.

The fact that neurologic manifestations were delayed by 5-9 days after the onset of influenza-like symptoms in these children, and CSF PCRs were negative in two patients tested, suggests that neurologic infection with influenza virus may not be directly responsible for the neurologic manifestations. Radiographic studies frequently demonstrate involvement of specifically the deep nuclei and basal ganglia, and patchy deep white matter involvement, suggesting an immunologic mechanism for the acute neurologic deterioration. Fortunately, the symptoms appear to respond favorably to time and treatment, with only modest neurologic impairment in one of the three children.

Infectious Disease Curbsides: What are They Worth?

Source: Grace C, et al. The complexity, relative value, and financial worth of curbside consultations in an academic infectious diseases unit. *Clin Infect Dis*. 2010;51:651-655.

How many times in your ID career have you been asked whether *Endolimax nana* requires treatment (just because many textbooks don't specifically state it does not)? Or whether that positive FTA needs to be treated? There are days where I joke I feel like a walking reference text. Curbside consultations play a significant role in infectious disease practice. Studies suggest that infectious diseases are the most heavily curbsided specialty service. And as reimbursements are increasingly diminished, and time constrained, there may be an increased demand for informal consultation from our primary care and other colleagues. But what is the value of that service, both in potential revenue but also in the recognition of the service provided?

The University of Vermont College of Medicine conducted a one-year prospective study of the burden and financial worth of curbside consultation on the university infectious disease service. Inpatient and outpatient consultations could be performed in person, by telephone or email, and were tracked on a daily basis. Each consult was assigned a CPT code (we all know those by heart now) based on the complexity of the case and the severity of the patient's illness. The Centers for Medicare & Medicaid Services' 2005 conversion factor for reimbursement, adjusted for the geographic area, was used to calculate the potential financial worth of the added work effort (at $37.89 per work RVU).

During the period of observation, 1,001 curbside consultations were performed an average of 2.84 per day, which seems just about right to me. One-third concerned inpatients, most of which were initial consultations and 84% were believed to be complex in nature. The remainder were regarding outpatient consultations, most of which also were initial consultations, 75% of which were considered complex in nature. Only a small number (< 4%) were follow-up consultations.

During the same time period, there were a total of 6,982 formal consultations performed, with an estimated work value of $459,265. Of these, 69% were inpatient consultations, most of which were follow-up consults, and 77% were considered complex in nature (presumably some of these were follow-up visits).

The estimated value of curbside consultations represented 17% of the total infectious disease services provided to the institution. The estimated value of the added work effort for curbside consultation was $93,979, which is essentially unreimbursed time on the part of the infectious disease specialists on service.

Curbsides are a time-honored practice for physicians; it's a way we share our experiences, how we learn from one other, and seek advice and assistance. However, an increasing number of reports indicate that infectious diseases are disproportionately affected by curbsides relative to other specialties. Various studies of curbside consultations have found that an infectious disease specialist performs anywhere from 23 to 121 curbside consultations per month, representing 0.5 to 2.4 of his or her formal consults.

The 17% in potential lost reimbursement to the infectious disease service identified above is, I suspect, fairly typical and, at a minimum, represents a loss of recognition of that effort and time. At our large multi-specialty clinic, I was recently asked to calculate the FTE effort of all physicians in my department, based solely on their "face time" with patients — with the assumption that physicians spend about 20% additional time doing charting, phone calls, etc ("non-face-time") (which is "built in" to their work effort). Factors such as time on call at night and weekends and curbside consultations were not included in these FTE estimates, although disproportionately require considerably more time and effort for infectious disease specialists than for other specialties. ■

PHARMACOLOGY WATCH

Supplement to *Clinical Cardiology Alert, Clinical Oncology Alert, Critical Care Alert, Hospital Medicine Alert, Infectious Disease Alert, Internal Medicine Alert, Neurology Alert, OB/GYN Clinical Alert, Primary Care Reports, Travel Medicine Advisor.*

Dabigatran Leading Race to Replace Warfarin

In this issue: FDA Advisory Committee recommends approval of dabigatran, safety of proton pump inhibitors, effectiveness of glucosamine and chondroitin, FDA Actions.

Advisory Committee recommends approval of dabigatran

In the race to find a drug to replace warfarin, Boehringer Ingelheim may have a leg up with the impending approval of dabigatran. The Cardiovascular and Renal Drugs Advisory Committee of the FDA unanimously recommended approval of the drug in September for the prevention of stroke and systemic clots in patients with atrial fibrillation. Dabigatran is a direct thrombin inhibitor that is given in a fixed dose twice a day and does not require monitoring. It is speculated that dabigatran will replace warfarin as the preferred anticoagulant in many settings, including many patients with atrial fibrillation. The approval was based on the Randomized Evaluation of Long-Term Anticoagulation Therapy trial, which was published last December. The study of more than 18,000 patients with atrial fibrillation showed that dabigatran given at a dose of 110 mg was similar in effectiveness to warfarin in prevention of strokes and systemic embolism, but had a significantly lower rate of major hemorrhage. A higher dose of 150 mg was associated with lower rates of stroke and systemic embolism compared to warfarin and similar rates of hemorrhage (*N Engl J Med* 2009;361:1139-1151). The FDA panel recommended approval of the higher dose, but was split on recommending the 110 mg dose. There was a slightly higher rate of heart attacks with dabigatran compared to warfarin, although the reviewers did not think this was serious enough to warrant holding the drug back. Dabigatran, once approved, will be marketed as Pradaxa®. Several companies are working on their own products to fill the same niche in what has been estimated to be a $10-20 billion market. Drugs in development include Bristol-Myers Squibb's apixaban and rivaroxaban, which is being jointly developed by Bayer Healthcare and Johnson & Johnson. Both drugs are direct inhibitors of Factor Xa. ■

Safety of proton pump inhibitors

Recent studies have suggested that proton pump inhibitors (PPIs) may negate some of the benefit of clopidogrel (Plavix®) in patients with cardiovascular (CV) disease. A new study refutes these findings, and at the same time raises more questions about the safety of PPIs. In a nationwide cohort study from Denmark, all patients discharged after first-time myocardial infarction (MI) were reviewed during 2000-2006. Of the more than 56,000 patients, 16% were rehospitalized for MI or stroke or experienced CV death. Nearly 25,000 patients were discharged on clopidogrel, of which nearly 30% received a concomitant PPI. Patients who were discharged on the combination of a PPI with clopidogrel or on a PPI alone had elevated but similar rates of death or rehospitalization for MI at 30 days (hazard ratio [HR], 1.29 for the combination [95% CI, 1.17-1.42]; HR, 1.29 for PPI alone [CI, 1.21-1.37]), indicating that

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the risk of a PPI with clopidogrel was no higher than a PPI alone. The authors conclude that there seems to be no significant interaction between PPIs and clopidogrel; however, PPIs may be associated with an increased risk for adverse CV outcomes after discharge. The authors postulate that the increased CV risk from PPIs is likely caused by unmeasured confounders (*Ann Intern Med* 2010;153:378-386). As pointed out in an accompanying editorial, this study may be very confusing for clinicians who have recently received warnings regarding the combination of clopidogrel with a PPI. It further highlights the potential risks of PPIs in patients with questionable or inappropriate indications for the drugs and the need for further studies into their risks and benefits (*Ann Intern Med* 2010;153:413-415). ■

Glucosamine and chondroitin

Millions of patients take glucosamine and chondroitin on a daily basis, hoping it is a safe alternative treatment for osteoarthritis. A new study suggests that the combination is ineffective but harmless. In a meta-analysis of 10 trials and more than 3800 patients, glucosamine, chondroitin, or the combination was compared to placebo with regard to pain scores and X-ray appearance of the hip and knee joint. None of the endpoints crossed the boundary of the minimal clinical important difference (95% credible intervals). The authors conclude that compared with placebo, glucosamine, chondroitin, and the combination do not reduce joint pain or have an impact on narrowing of joint space of the hip or knee. They further state that insurers should not cover the cost of these preparations, but since there is little harm, patients may wish to continue buying and taking it (*BMJ* 2010;341:c4675). ■

FDA Actions

The FDA has announced that it will significantly restrict the use of rosiglitazone (Avandia®) to patients with type 2 diabetes who cannot control the disease on other medications. The FDA had the option of removing the drug from the market, a move that was recently taken by the European Medicines Agency; however, the agency decided to limit access at least for now. Rosiglitazone has been associated with an elevated risk of cardiovascular events.

The FDA has approved fingolimod (Gilenya®), the first oral drug to reduce relapses and delay disability progression in patients with relapsing-remitting multiple sclerosis. The drug is the first of a new class called sphingosine 1 phosphate receptor modulators. Patients need to be closely monitored for symptomatic bradycardia. Fingolimod will be marketed by Novartis Pharmaceuticals.

The Endocrinologic and Metabolic Drugs Advisory Committee of the FDA has voted against recommending approval of lorcaserin hydrochloride for the treatment of obesity (see September *Pharmacology Watch*). Although the drug was shown to be effective, resulting in at least a 5% body weight loss for half of patients taking the drug over 1 year, there were concerns over valvular heart disease. Arena Pharmaceuticals argued that valvulopathy was not a significant issue and that they met the FDA's predefined goals for safety. The FDA is not required to follow subcommittee recommendations, however it usually does.

The same subcommittee also recently reviewed the weight-loss drug sibutramine (Meridia-Abbott Laboratories) and delivered a **split vote on whether sibutramine should stay on the market.** Sibutramine has been the subject of controversy since last November when initial data from the Sibutramine Cardiovascular Outcomes trial revealed a higher rate of cardiovascular disease associated with the drug. The full study was published in September and showed that cardiovascular events were observed significantly more frequently in the sibutramine group than in the placebo group (11.4% vs 10.0%; $P = 0.02$). The rate of cardiovascular death or death from any cause, however, was no different in the two groups (*N Engl J Med* 2010;363:905-917). The FDA subcommittee voted 8-8, with 8 members voting to remove the drug from the market and the other 8 voting to allow the drug to remain on the market with tougher warnings and a restricted distribution pattern. The FDA vote is expected later this fall.

The **FDA has approved pegloticase for the treatment of refractory gout in patients who have not responded to or can't tolerate conventional therapy.** The drug is administered intravenously every 2 weeks. It appears to work by metabolizing uric acid to allantoin, which is then cleared through the kidneys. The approval was based on two 6-month trials in more than 200 patients that showed the drug reduces uric acid levels and reduces uric acid deposits in joints and soft tissue. About one in four patients will experience severe allergic reactions to the infusion, so patients should be given an antihistamine and a corticosteroid prior to administration. The drug was not studied in patients with congestive heart failure and should not be used in this population. Savient Pharmaceuticals will market pegloticase as Krystexxa™. ■